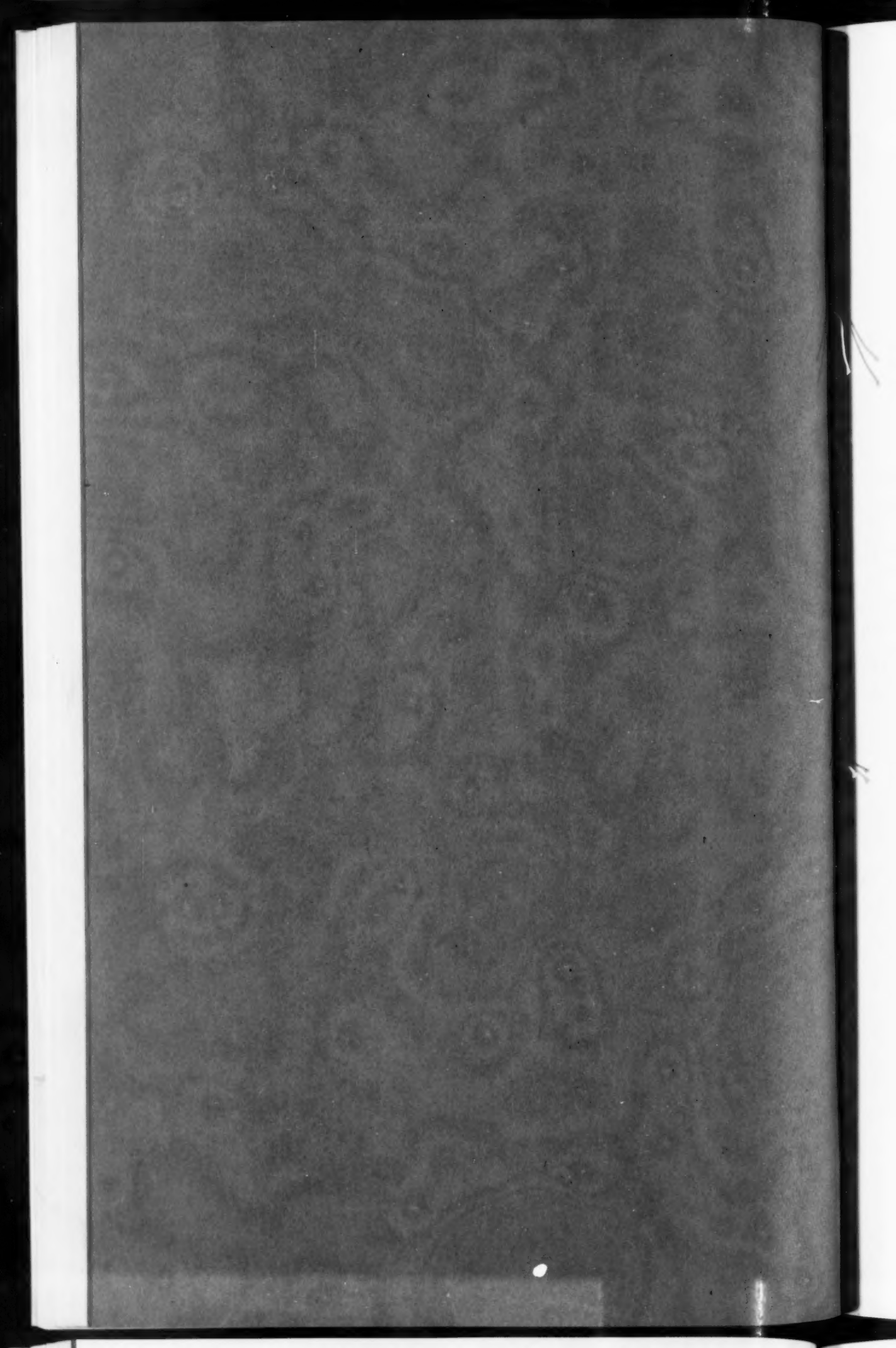
VOLUME 59 NUMBER 6

ARCHIVES OF NEUROLOGY AND PSYCHIATRY

JUNE 1948

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $10.00

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, under the Act of Congress of March 3, 1879. Additional entry at Nashville, Tennessee.



Archives of Neurology and Psychiatry

VOLUME 59 JUNE 1948 NUMBER 6

ACTIVATION OF SEIZURES AND ELECTROENCEPHALOGRAPHIC DISTURBANCES IN EPILEPTIC AND IN CONTROL SUBJECTS WITH "METRAZOL"

CHARLES CURE, M.D.
THEODORE RASMUSSEN, M.D.
AND
HERBERT JASPER, M.D.
MONTREAL, CANADA

ANALYSIS of types of epileptic seizures is sometimes difficult, and often uncertain, owing to infrequent opportunities for the observation of the attacks under conditions which permit an accurate description of their manner of onset and pattern of progression. Hyperventilation has long been used as a simple and reliable method of inducing attacks in certain patients (especially those with idiopathic petit mal epilepsy); but this method is not of general value, since it induces seizures only in about 10 to 30 per cent of unselected epileptic patients. The pitressin hydration regimen of McQuarrie has been found more successful for the controlled induction of seizures, but it has the disadvantage of being a prolonged (twenty-four to forty-eight hours), disagreeable and often painful procedure. More important, when a seizure does occur, its onset is frequently missed because its time of occurrence is unpredictable, Alcohol, which may also induce seizure in certain patients, is less disagreeable, but even more uncertain, than hydration.

The interseizure epileptiform discharges recorded and localized by means of the electroencephalogram have been a most important recent addition to the armanentarium of diagnostic aids in epilepsy. Even with this highly sensitive objective method, the nature of the seizures in a fair percentage of patients, variously estimated by different authors to be between 10 and 50 per cent, cannot be determined. This percentage is reduced by the combination of hyperventilation and hydration with electroencephalography, but there is needed a rapid and reliable method of inducing both the electroencephalographic signs and the clinical onset of a patient's habitual seizure under controlled conditions.[1]

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

1. Intravenous administration of insulin was tried in the early part of the present study. It was found to increase epileptiform abnormality in the electro-

(Footnote continued on next page)

As an addition to these methods, the injection of "metrazol" (pentamethylenetetrazol) was suggested by the work of Langeluddeke[2] and von Meduna,[3] and, more recently, by the studies of Goldstein and Weinberg[4] and Sal y Rosas,[5] who used the drug as a clinical diagnostic aid without the electroencephalogram. Von Meduna found that most epileptic patients reacted with a convulsion when given 200 to 300 mg. by his method. All the patients required less than 500 mg., while none of the nonepileptic subjects (23 patients) reacted with a convulsion to less than 500 mg.; the greatest amount required was 600 to 850 mg. Roismiser[6] expressed the belief that the test was useful in the medicolegal diagnosis of epilepsy. He found that 38 epileptic subjects responded with a typical seizure when given 300 mg. or less, whereas 18 nonepileptic subjects required a larger dose. Larue and Pelletier[7] found the "metrazol" test superior to hydration. Their method was to give 2 cc. of a 10 per cent solution (200 mg.) and repeat it at intervals if no seizure was produced. They stated that the dose must be above 3 cc. (300 mg.) to produce a convulsion in a nonepileptic patient.

Other investigators have concluded that "metrazol" was misleading and without value in the diagnosis of epilepsy. Janz[8] reported positive results in 54 per cent of 33 epileptic patients given varying doses of the drug (300 to 600 mg.), whereas 37 per cent of a group of nonepileptic

---

encephalogram, especially in the 3 per second wave and spike petit mal disorders, and to increase the sensitivity to hyperventilation, as observed previously by Gibbs, Gibbs and Lennox (Influence of the Blood Sugar Level on the Wave and Spike Formation in Petit Mal Epilepsy, Arch. Neurol. & Psychiat. **41**:1111-1116 [June] 1939) and others. However, the tendency of insulin to cause abnormal discharges to appear in the electroencephalograms of nonepileptic persons, and the great individual differences observed in sensitivity to insulin, make it generally an unreliable aid in the diagnosis of epilepsy, except for certain patients whose attacks seem to be related to periods of hypoglycemia.

2. Langeluddeke, A.: Ueber Cardiazolkrampfe, Ztschr. f. d. ges. Neurol. u. Psychiat. **161**:347-348, 1938.

3. von Meduna, L.: Diagnostico da epilepsia, Rev. neurol. e psychiat. de São Paulo **5**:101-109, 1939.

4. Goldstein, H. H., and Weinberg, J.: Metrazol as a Diagnostic Aid in Epilepsy, Am. J. Psychiat. **96**:1455-1458, 1940.

5. Sal y Rosas, F.: Diferencias de la susceptibilidad convulsiva experimental en el Peru y en los paises Europeos, Rev. mex. psiquiat., neurol. y med. leg. **10**:3-16, 1943.

6. Roismiser, I.: El diagnóstico de la epilepsia mediante el pentametilenetetrazol, Semana med. **1**:310-314, 1943.

7. Larue, G. H., and Pelletier, A.: Métrazol et épilepsie, Laval méd. **7**:22-24, 1942.

8. Janz, H. W.: Zur diagnostischen Verwertbarkeit der Cardiazolkrampfe, München. med. Wchnschr. **84**:471, 1937.

patients also reacted with a convulsion. Duensing[9] was able to produce seizures in only 21 (68 per cent) of a series of 31 epileptic patients with 300 mg., whereas the incidence of seizures in feebleminded subjects was 50 per cent with the same dose and 26 per cent in patients without signs of organic disease of the central nervous system. Coloma[10] was unable to find a dose that was nonconvulsant for nonepileptic persons and convulsant for patients with epilepsy.

Langeluddeke[2] stated the belief that seizures induced with "metrazol" were the same as the patient's spontaneous or habitual attacks and that the test was useful in differentiating essential and symptomatic epilepsy. He admitted that the test must be interpreted with great caution, since in his series of 53 nonepileptic patients there was an incidence of seizures of 23 per cent even when the dose was less than 300 mg. De Wildt[11] also emphasized the similarity of spontaneous and artificial attacks induced with "metrazol." Muyle,[12] discussing the value of the "metrazol" test, expressed despair of finding a dose pathognomonic for epilepsy but expressed the opinion that the convenience of the test and the higher percentage of seizures in epileptic patients than in nonepileptic patients indicated that further investigation was warranted. Goldstein and Weinberg[4] administered subcutaneously 500 mg. per hundred pounds (45 Kg.) of body weight to 34 epileptic patients with an incidence of seizures of 47 per cent, while of 84 schizophrenic patients, only 1 reacted with a convulsion. On reexamination this patient presented signs of organic cerebral disease.

It was evident from the consideration of these results that the induction of seizures with "metrazol" deserved further investigation as a method for the activation of latent electroencephalographic epileptiform activity and clinical seizures peculiar to the patient. These studies were begun by one of us (T.R.) in 1941 but were discontinued for four and a half years, during the war.

CLINICAL MATERIAL AND METHODS

Material.—The patients studied in this series were referred to the electroencephalographic laboratory of the Montreal Neurological Institute, either from the neurologic and neurosurgical services of this institute or from outside physicians and hospitals. There was a total of 130 epileptic patients and 42 nonepileptic,

9. Duensing, F.: Darf der Cardiazol-Krampfanfall diagnostisch verwertet werden? München. med. Wchnschr. **84**:1011-1015, 1937.

10. Coloma, T. A.: El cardiazol en el diagnostico de la epilepsia, Med. españ. **56**:3-7, 1943.

11. de Wildt, D. C. de Ryter: Behandeling van genuine epilepsie, Geneesk. tijdschr. v. Nederl.-Indië **80**:2579-2584, 1940; Biol. Abstr. **15**:933-934, 1941.

12. Muyle, G.: De la valeur de l'épreuve au cardiazol en tant que test diagnostique de l'épilepsie, J. belge de neurol. et de psychiat. **38**:525-529, 1938.

control, subjects. Only epileptic patients for whom the diagnosis was well established were included. Twenty-seven additional patients studied were excluded from this report because of uncertain clinical diagnosis or, in a few instances, because of technically unsatisfactory electroencephalographic records.

The electroencephalographic examinations were carried out according to the standard technics used in these laboratories.[13] The epileptic patients were classified on the basis of the pre-"metrazol" electroencephalographic record as follows:

GROUP 1: Localized Spikes or Sharp Waves (56 patients): This type of activity characterizes superficial focal epileptogenic lesions of the convexity of the cortex.

GROUP 2: Bilateral Random and Rhythmic Sharp Waves (18 patients): This type of activity, in our experience, has usually been associated with deep-seated epileptogenic lesions of the inferior surface of the temporal lobe, the island of Reil, the orbital or mesial surface of the frontal lobe or subcortical structures. These wave complexes, when rhythmic, occur most commonly at frequencies of either 2 to 2.6 or 4 to 6 cycles per second. This type includes the so-called petit mal variant pattern and some of the psychomotor patterns of Gibbs, Gibbs and Lennox.[14] The deep-seated origin of these electroencephalographic disturbances has been confirmed by Walter and Dovey,[15] Cobb[16] and Lennox and Brody.[17]

GROUP 3: Diffuse Random Abnormality (13 patients): This type is characterized by generalized paroxysmal, rapid, multiple spike disturbances or diffuse, slow and sharp waves. Some of the patients in this group were shown to have diffuse organic abnormalities of the brain, while others had seizures of uncertain origin, but usually without signs of a localized cerebral lesion. Some may well be considered to have had idiopathic epilepsy.

GROUP 4: Bilaterally Synchronous 3 per Second Waves and Wave Spike Complexes (22 patients): This is the classic eletroencephalographic pattern of idiopathic epilepsy common in cases of petit mal attacks or major generalized convulsions beginning with loss of consciousness. It is distingusihed from those bilateral disturbances described for group 2 by the precise regularity of its 3 per second rhythm, its perfect bilateral synchrony and symmetry from homologous areas of the two hemispheres and special features of the wave and spike complex which distinguish it from various types of the pseudo wave and spike pattern, sometimes confused with the true idiopathic forms.

The epileptic patients were also classified on a clinical basis with respect to the history and form of the seizure, more or less independently of the electroencephalographic pattern. For this purpose, the following preliminary general grouping of patients was employed.

---

13. Jasper, H. H., and Kershman, J.: The Electroencephalographic Classification of the Epilepsies. Arch. Neurol. & Psychiat. **45**:903-943 (June) 1941.

14. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy, Arch. Neurol. & Psychiat. **39**:298-314 (Feb.) 1938.

15. Walter, W. G., and Dovey, V. J.: Electroencephalography in Cases of Sub-Cortical Tumours, J. Neurol., Neurosurg. & Psychiat. **7**:57-65, 1944.

16. Cobb, W. A.: Rhythmic Slow Discharges in the Electroencephalogram, J. Neurol., Neurosurg. & Psychiat. **8**:65-78, 1945.

17. Lennox, M., and Brody, B. S.: Paroxysmal Slow Waves in the Electroencephalograms of Patients with Epilepsy and with Subcortical Lesions, J. Nerv. & Ment. Dis. **104**:237-248, 1946.

GROUP A: Focal Cortical Seizures (51 patients): This group consists of patients with focal cortical seizures arising from a wide variety of local cortical regions, as described by Penfield and Erickson.[18] In addition to patients with focal sensory or motor onset, it includes patients with visual, auditory, vertiginous and hallucinatory auras, as well as patients with automatic behavior, often described as "psychomotor." Patients with "psychomotor" seizures, in our experience, usually have focal epileptogenic lesions in one temporal region.

GROUP B: Idiopathic Epilepsy (38 patients): The following criteria were used in the selection of this group: (*a*) a clear genetic background; (*b*) occurrence of generalized, nonfocal attacks in the absence of known organic cause, particularly attacks of typical petit mal, with or without major seizures, and with onset before the age of 20, and (*c*) a classic, bilaterally synchronous wave and spike electroencephalographic pattern.

GROUP C: Generalized Cerebral Seizures, Cause Unknown (41 patients): This is a miscellaneous group of patients who could not be placed in either of the preceding two groups on the basis of available data.

Methods.—"Metrazol" was administered by three different methods: rapid intravenous injection, intramuscular injection and slow intravenous injection. The attempt was made to adjust the dose and mode of administration so as to produce clear activation of the patient's characteristic epileptiform disturbance in the electroencephalogram and the aura or initial onset of the seizure, if possible without producing a major generalized convulsion.

A change in the electroencephalogram following the injection of "metrazol" was considered significant if it consisted in the appearance of definite epileptiform discharges or an increase in their number of voltage. The occurrence of low voltage, rapid waves or bursts of low voltage, 3 to 6 per second waves, was not considered a significant response. The clinical response was considered of diagnostic significance if the patient's habitual aura or onset of the seizure was reproduced.

Further details of procedure are given under the separate presentation of the three methods of administering "metrazol."

RAPID INTRAVENOUS ADMINISTRATION

Procedure.—Following the method introduced by von Meduna, rapid intravenous injection of small amounts of "metrazol" was used in the first series of 55 epileptic patients and 6 nonepileptic, control, subjects. For this initial study, epileptic patients were selected who showed clearly focal electroencephalographic abnormality (35 patients), bilaterally synchronous wave and spike patterns (15 patients) or diffuse, random epileptiform discharges (5 patients). Patients with other types of electroencephalograms (normal or borderline and bilateral sharp waves) were not studied by this method.

When these patients were classified according to the type of seizure pattern and the clinical history, 20 were shown to have focal attacks; 15, idiopathic epilepsy, and 20, nonfocal, generalized seizures of undetermined cause.

The nonepileptic patients included 2 with schizophrenia, 1 with post-traumatic headache, a sleepwalker, the twin of a patient with idiopathic epilepsy, and the father of a patient with migraine.

---

18. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941, pp. 14-19.

The majority of the epileptic patients and the control subjects were given, by rapid intravenous injection (within three to five seconds), 1.1 or 1.2 cc. of a 10 per cent solution of "metrazol" per hundred pounds (2.4 or 2.6 mg. per kilogram) of body weight. A few of the early patients received doses as small as 0.5 cc. per hundred pounds (1.1 mg. per kilogram), and a few of the later patients received as much as 2 cc. per hundred pounds (4.4 mg. per kilogram). Electroencephalograms were taken before, during and after the injection. Both subjective and objective responses of the patient were carefully noted.

Results.—Epileptiform discharges in the electrocephalogram were induced or increased in 27 of the 55 epileptic patients (49 per cent). The latent period for the appearance of the epileptic discharge after completion of the injection was eight to thirty-two seconds. The results according to the electroencephalographic classification are summarized in table 1 and may be described as follows:

Localized Spikes or Sharp Waves (35 patients): Activation of the electroencephalographic activity occurred in 14 subjects (40 per cent), but in only 8 was it of a focal character, whereas in the other 6 patients the epileptiform abnormality appeared simultaneously from the two hemispheres. The pre-"metrazol" record for 3 of these 6 patients showed considerable bitemporal abnormality, in addition to a unilateral temporal focus. A fourth patient, with a frontal focus, had also considerable bilateral abnormality in the pre-"metrazol" electroencephalogram. On the electroencephalograms of the remaining 21 patients (60 per cent) the "metrazol" injection produced no apparent effect.

Of the patients showing focal activation, 1 experenced his habitual aura, and in another it progressed to a major seizure. Two of the patients with bilaterally simultaneous onset of electroencephalographic disturbance experienced their habitual aura, and 2 had nonfocal, generalized convulsions associated with high voltage, multiple spike activity in the electroencephalogram. These convulsions were apparently regular "metrazol" seizures. In an additional 3 patients the habitual aura was reproduced without a detectable change in the electroencephalogram.

Diffuse Random Abnormality (5 patients): One of the 5 patients in this group exhibited a small burst of irregular, high voltage waves with bilaterally simultaneous onset, while no change was observed in the electroencephalograms of the other 4 patients, although the habitual aura was reproduced in 1 instance.

Bilaterally Synchronous Wave and Spike Patterns (15 patients): One or more bursts of typical 3 per second wave and spike discharges were produced in the electroencephalograms of 12 of the 15 patients in this group (80 per cent), and no significant change occurred in those of the other 3 patients. Clinical seizures followed the electroencephalographic abnormality in 5 patients, or in 33 per cent of the total group. Four had major convulsive attacks, and 1, a typical "petit mal" seizure.

TABLE 1.—*Results of Administration of "Metrazol" Correlated with Electroencephalographic Classification of Epileptic Seizures*

Type of Electroencephalographic Abnormality	Rapid Intravenous Injection				Intramuscular Injection				Slow Intravenous Injection			
	No. of Patients	Average Dose, Mg.	Activation		No. of Patients	Average Dose, Mg.	Activation		No. of Patients	Average Dose, Mg.	Activation	
			Eeg	Clinical			Eeg	Clinical			Eeg	Clinical
Localized spikes or sharp waves	35	140	14 (40%)	9 (26%)	7	370	5 (71%)	4 (57%)	14	260	13 (93%)	10 (71%)
Bilateral random and rhythmic sharp waves	—	—	—	—	7	315	7 (100%)	2 (29%)	11	240	11 (100%)	6 (55%)
Diffuse random abnormality	5	120	1 (20%)	1 (20%)	1	380	1 (100%)	1 (100%)	7	305	4 (57%)	3 (43%)
Bilaterally synchronous wave and spike pattern	15	120	12 (80%)	5 (33%)	2	400	1 (50%)	1 (50%)	5	200	5 (100%)	3 (60%)
Normal or borderline normal electroencephalogram	—	—	—	—	8	360	3 (38%)	3 (38%)	13	295	7 (54%)	6 (46%)
Total no. of patients	55	130	27 (49%)	13 (23%)	25	355	17 (68%)	11 (44%)	50	265	40 (80%)	28 (56%)

TABLE 2.—*Results of Administration of "Metrazol" in Epileptic Patients (Correlated with Clinical Type of Seizures) and in Control Subjects*

Clinical Type of Seizure	Rapid Intravenous Injection				Intramuscular Injection				Slow Intravenous Injection			
	No. of Patients	Average Dose, Mg.	Activation		No. of Patients	Average Dose, Mg.	Activation		No. of Patients	Average Dose, Mg.	Activation	
			Eeg	Clinical			Eeg	Clinical			Eeg	Clinical
Focal seizures	20	140	9 (45%)	6 (30%)	10	400	6 (60%)	6 (60%)	21	275	15 (71%)	14 (67%)
Idiopathic epilepsy	15	120	12 (80%)	5 (33%)	7	270*	5 (71%)	3 (43%)	16	230	16 (100%)	9 (56%)
Generalized cerebral seizures	20	130	6 (25%)	4 (20%)	8	370	6 (75%)	2 (25%)	13	275	9 (69%)	5 (38%)
Total no. of patients	55	130	27 (46%)	13 (23%)	25	355	17 (68%)	11 (44%)	50	265	40 (80%)	28 (56%)
Control subjects	6	150	0	0	5	370	0	0	31	390	8 (26%)	1 (3%)

*This figure includes that for a 4 year old boy who received only 75 mg., the average dose for the remaining 6 patients being 300 mg.

The results according to the clinical classification of the patients are summarized in table 2. With the rapid administration of "metrazol" in these small doses, patients with idiopathic epilepsy showed a much higher frequency of the electroencephalographic activation (80 per cent) than did patients with focal seizures (45 per cent). The patients in the miscellaneous group, with generalized seizures of unknown cause, showed the lowest incidence of both electroencephalographic and clinical activation (25 and 20 per cent respectively). There was no significant difference in the incidence of clinical activation between the group with idiopathic and the group with focal epilepsy.

Nonepileptic, control, subjects (6 patients): No significant clinical or electroencephalographic changes were observed in the nonepileptic, control, subjects (table 2). Subjectively, the only experience reported by the patients was a momentary sensation of dizziness, described by 5 of the subjects.

Summary: Rapid intravenous injections of small doses of "metrazol" activated characteristic epileptiform discharges in the electroencephalograms of 80 per cent of the patients with bilaterally synchronous wave and spike epilepsy. Of the group with focal seizures, however, only 23 per cent showed activation of their focal discharges, while in 17 per cent there was produced an epileptiform discharge of bilateral, nonfocal onset.

Generalized "metrazol" seizures were produced in 2 patients (5 per cent). Thus, these small doses of metrazol, rapidly administered, could occasionally produce generalized "metrazol" seizures in patients with habitual focal epilepsy. However, they failed to produce a significant change in the electroencephalograms of 60 per cent of these patients.

In a further effort to activate focal epileptogenic lesions, it seemed advisable to change the mode of administration, rather than to increase the dose, since it was probable that the latter would increase the percentage of generalized "metrazol" seizures, and hence confuse the diagnosis.

INTRAMUSCULAR ADMINISTRATION

Procedure.—Owing to the extreme rapidity with which a generalized seizure may be produced by rapid intravenous injection of "metrazol," it was felt that a slower mode of administration might make it possible to study the onset of the seizure more completely. Consequently, in the next series of 25 epileptic patients and 5 nonepileptic, control, subjects, "metrazol" was administered intramuscularly.

The nonepileptic patients included 2 patients with neuroses, 1 patient with hysteria, 1 patient with syringobulbia and 1 patient with an old head injury, without residual disability.

"Metrazol," in 10 per cent solution, was given by intramuscular injection in doses of 2.5 to 3.1 mg. per hundred pounds (5.5 to 6.8 mg. per kilogram) of body weight.

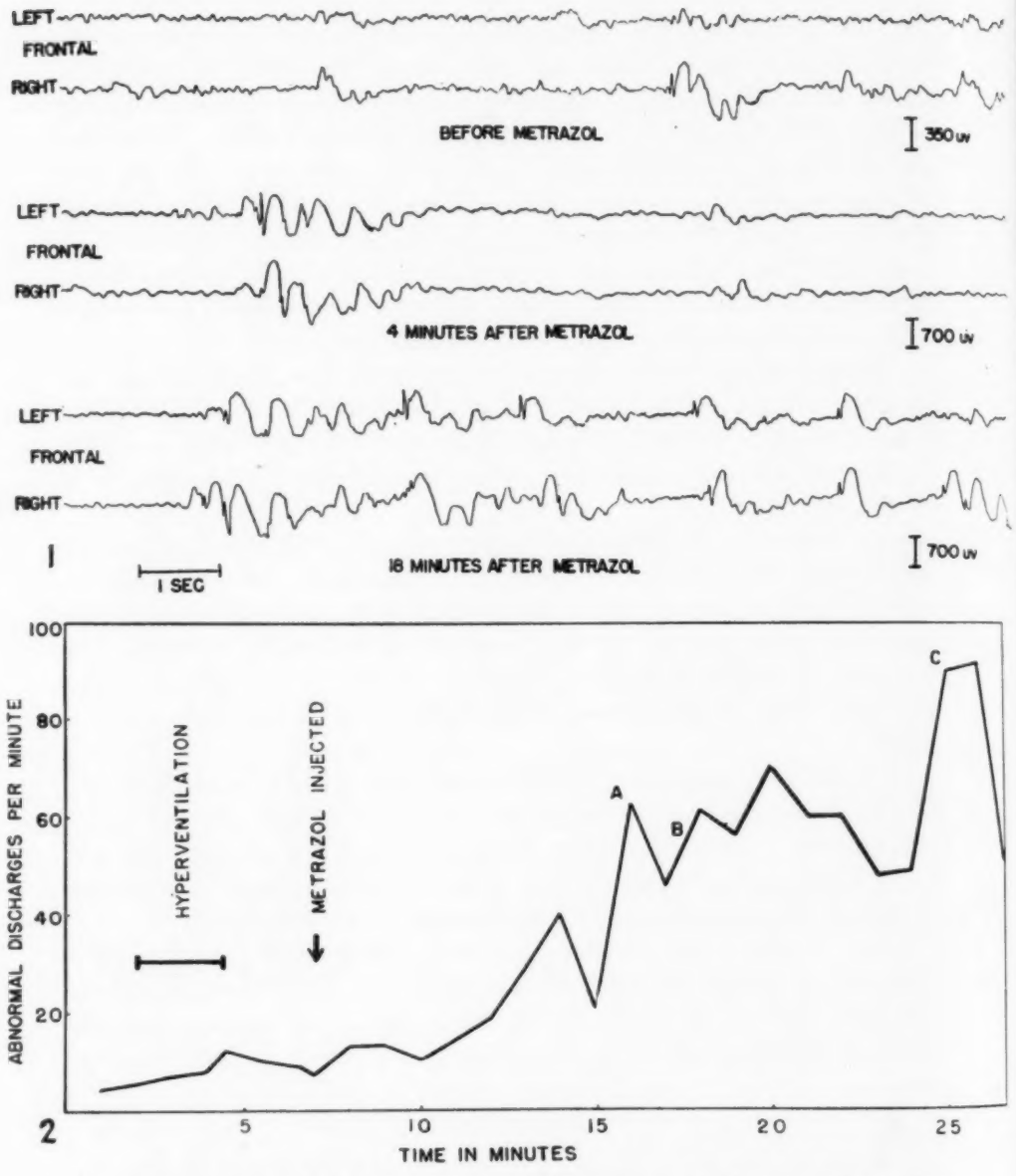


Fig. 1.—Effects of intramuscular administration of 300 mg. (7.5 mg. per kilogram of body weight) of "metrazol" to L. M., a girl aged 15 years, with a history of major nonfocal seizures following meningitis.

1 shows sample tracings before and after injection of the "metrazol." Note the increase in voltage of the abnormal wave complexes, the increase in duration of the bursts and the similarity in the wave form. *2* is a graph showing the increase in number of the abnormal discharges following the injection of "metrazol." At *A* a patchy erythema of the trunk was noted; at *B* spasmodic colonic movements of the extremities occurred, and at *C* these movements were considerably increased.

Results.—Epileptiform discharges were induced or increased in 17 of the 25 epileptic patients (68 per cent). These electroencephalographic changes appeared after a delay of ten to fifteen minutes following the intramuscular injection (fig. 1). The results according to electroencephalographic and clinical classifications are summarized in tables 1 and 2. This group was too small for detailed consideration to be of significance, since intramuscular injections were soon discontinued, as the advantages of the method of slow intravenous injection became apparent. The intramuscular method, however, was superior to the rapid intravenous method, since activation occurred more gradually and in none of the patients with focal epilepsy was a generalized "metrazol" effect produced. In addition, the incidence of both electroencephalographic and clinical activation was, in general, somewhat higher with the intramuscular method. As in the previous group, none of the 5 nonepileptic, control, subjects receiving the intramuscular injections showed any significant electroencephalographic or clinical disturbance.

SLOW INTRAVENOUS ADMINISTRATION

Procedure.—The intravenous injections were given slowly, over a period of five to twenty minutes, to 50 epileptic and 31 nonepileptic (control) subjects. The latter included 21 patients with schizophrenia, 3 with psychoneurosis, 2 with psychosis and mental deficiency, 1 with manic-depressive psychosis and 4 normal subjects (staff).

The majority received a 2 per cent solution at the rate of 40 mg. per minute until significant electroencephalographic changes occurred, until the patient's aura or onset of seizure was produced or until a maximum of 400 mg. had been given. In a few instances the rate was reduced to 20 mg. or increased to 50 mg. per minute. Concentrations of solutions between 4 and 10 per cent were also tried in a few instances.

Injections were made intermittently at thirty second intervals, each dose being given within about five seconds. Hyperventilation was used in some instances after the injection of a maximum dose of "metrazol" when it was necessary to enhance the activation of epileptiform discharge. No attempt was made to induce a major clinical attack in some cases, although such seizures occasionally occurred. Continuous electroencephalographic records and careful observations on the patients were made throughout, and the injection was stopped when a clear increase in epileptiform discharge was seen in the electroencephalogram. This was often associated with induction of the patient's aura or an aborted onset of the patient's attack.

Results.—An epileptiform discharge was induced or increased in 40 of the 50 epileptic patients (80 per cent). "Metrazol" induced a definite increase in epileptiform discharge in 33 (89 per cent) of the 37 epileptic patients who showed a well defined abnormality in their pre-"metrazol" electroencephalograms. Definite epileptiform electroencephalographic disturbances were induced in 7 (54 per cent) of the 13 epileptic patients with normal or borderline normal pre-"metrazol" records. In

28 (56 per cent) there were also produced clinical signs of an abortive onset or a complete epileptic seizure. The clinical and electroencephalographic results for each group of epileptic patients classified according to the pre-"metrazol" electroencephalogram are presented in table 1.

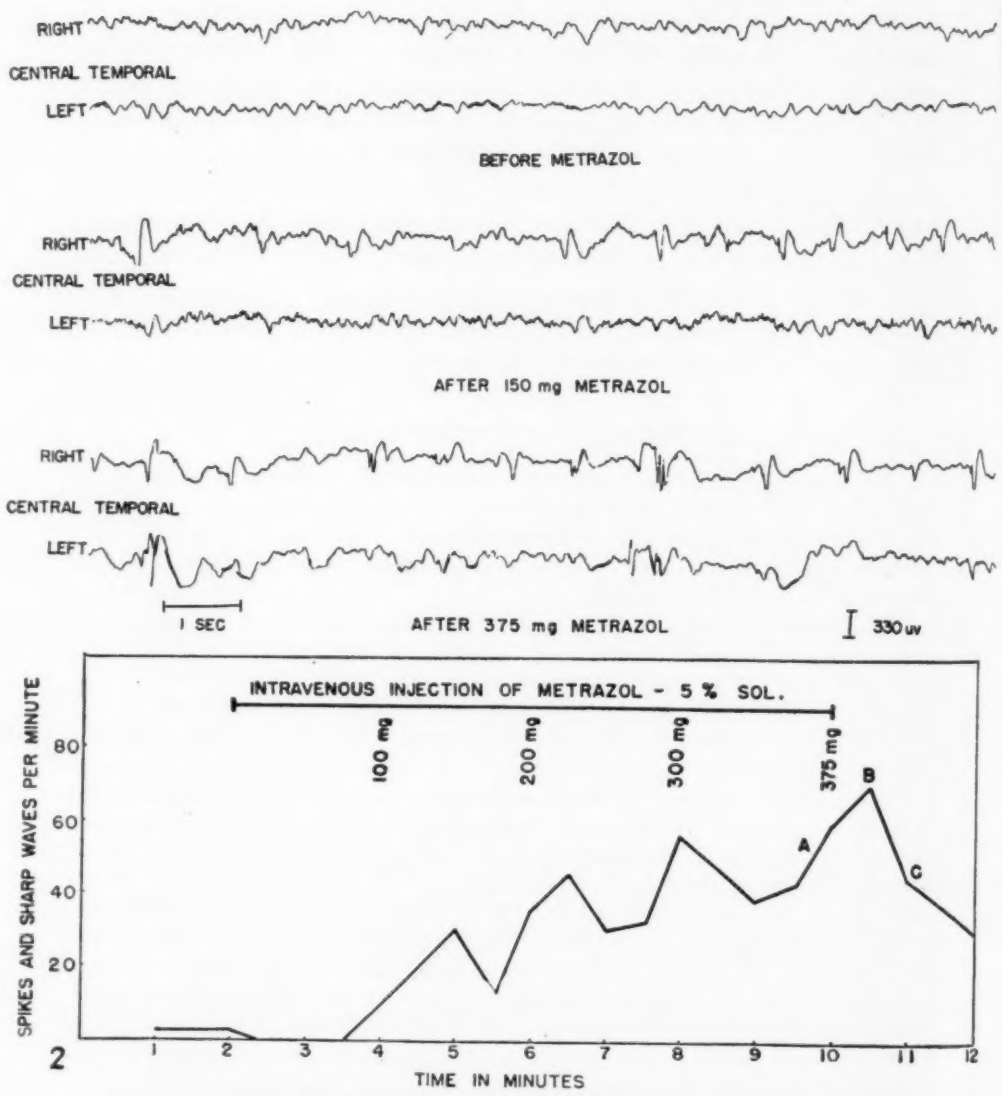


Fig. 2.—Effects of slow intravenous administration of 357 mg. of "metrazol" (50 mg. per minute) to R. M., a youth aged 15 years, with a history of focal seizures starting during an attack of tonsillitis, at the age of 10 months. There was a focus of sharp waves in the right temporal region.

1 shows sample tracings before and during the injection of "metrazol." *2* is a graph showing the increase in frequency of the sharp wave discharges produced by the "metrazol." At *A* jerking of the left arm began; at *B*, with increasing bilateral discharges, there were jerking movements of both arms, and at *C*, with beginning cessation of the discharges, convulsive movements stopped.

Localized Spikes or Sharp Waves (14 patients): The slow administration of "metrazol" clearly activates a focal epileptogenic lesion selectively before significant generalized epileptiform changes occur. This is shown by the fact that all the 13 patients with focal epilepsy in whom there was definite induction of epileptic activity manifested it first by an increase in the discharges from the habitual focus (fig. 2). In no instance was there a generalized onset, nor were bilaterally synchronous wave and spike discharges produced. Of the 10 patients in whom clinical activation occurred, 6 experienced their habitual aura alone, and in an additional 4 patients the activation proceeded to a seizure which resembled the pattern of the habitual attacks. The remaining 4 patients showed no significant clinical response.

The patient who failed to show either electroencephalographic or clinical activation received the usual intravenous injection of 400 mg. at the rate of 40 mg. per minute, followed by injection of an additional 200 mg. at the rate of 80 per minute. This patient had had only two attacks, the first occurring one month before the electroencephalographic examination.

Bilateral Random and Rhythmic Sharp Waves (11 patients): Activation of this type of discharge was produced in the electroencephalograms of all the patients in this group. In 6 (55 per cent) there was clinical activation as well. The latter consisted in the reproduction of the patient's typical myoclonic jerks (4 patients), petit mal (1 patient) and the habitual sensory aura (1 patient).

Diffuse Random Abnormality (7 patients): An increase in generalized epileptiform abnormality was produced in the electroencephalograms of 4 patients (57 per cent). For 2 of these, the types of generalized disturbance present in the pre-"metrazol" record was increased, whereas the third patient showed high voltage, 6 per second waves after the administration of "metrazol," although these were not present in the resting record; and the fourth patient showed typical bilaterally synchronous wave and spike discharges after injection of "metrazol," whereas the pre-"metrazol" record had shown only a high voltage, multiple spike type of epileptiform abnormality. One patient had a generalized seizure with bilateral onset, both clinically and as judged by the electroencephalogram. In a second patient the sensory aura was clearly reproduced, although there were no detectable changes in her electroencephalogram. Electrocorticograms made at operation later showed that this patient had a definite focal epileptiform abnormality, although the previous recordings from the scalp had shown only a generalized disturbance. In the third patient in whom there was a clinical response the typical aura was likewise reproduced.

Bilaterally Synchronous Wave and Spike (5 patients): All 5 of these patients showed marked activation of the wave and spike discharges with reproduction of the characteristic wave form (figs. 3, 4 and 5). This tended to occur somewhat earlier in the course of the injection than was the case with patients of the other groups, with the result that the average dose of "metrazol" was lower in this group than in any of the others. This would seem to increase the significance of the electroencephalographic activation in 100 per cent of the patients, even though the group consisted of only 5 patients.

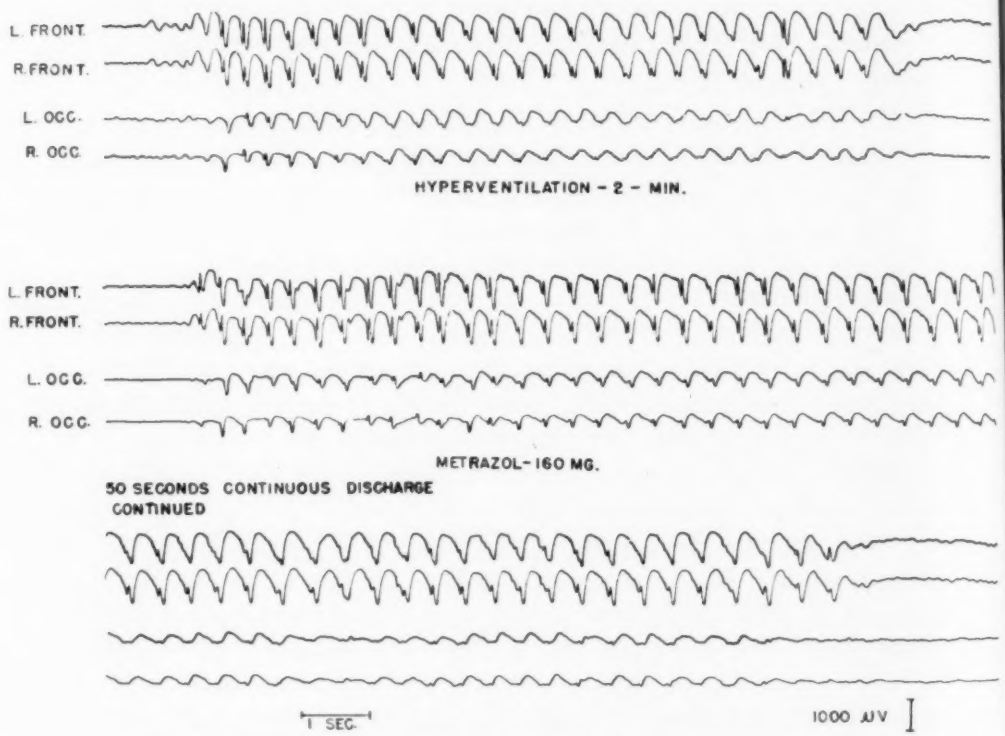


Fig. 3.—Effect of slow intravenous injection of 200 mg. of "metrazol" (2 per cent solution, given at a rate of 20 mg. every half-minute) in R. F., a boy aged 13 years, with a history of petit mal and major nonfocal seizures since the age of 10 years. Note the faithful reproduction of the wave form and the increase in length of the discharge.

Clinical activation occurred in 3 patients (60 per cent). One patient's typical myoclonic seizure was reproduced; a second patient had a classic petit mal attack, and the third had a generalized seizure with a clinically bilateral onset following a series of wave and spike discharges. In the remaining 2 patients there was no obvious clinical response, although a definite increase in the electroencephalographic disturbance was noted in each.

Normal or Borderline Normal Activity (13 patients): Epileptiform activity appeared in the electroencephalograms of 7 patients (54 per cent) as a result of the slow intravenous administration of "metrazol." In 3 of these records, typical 3 per second, bilaterally synchronous wave

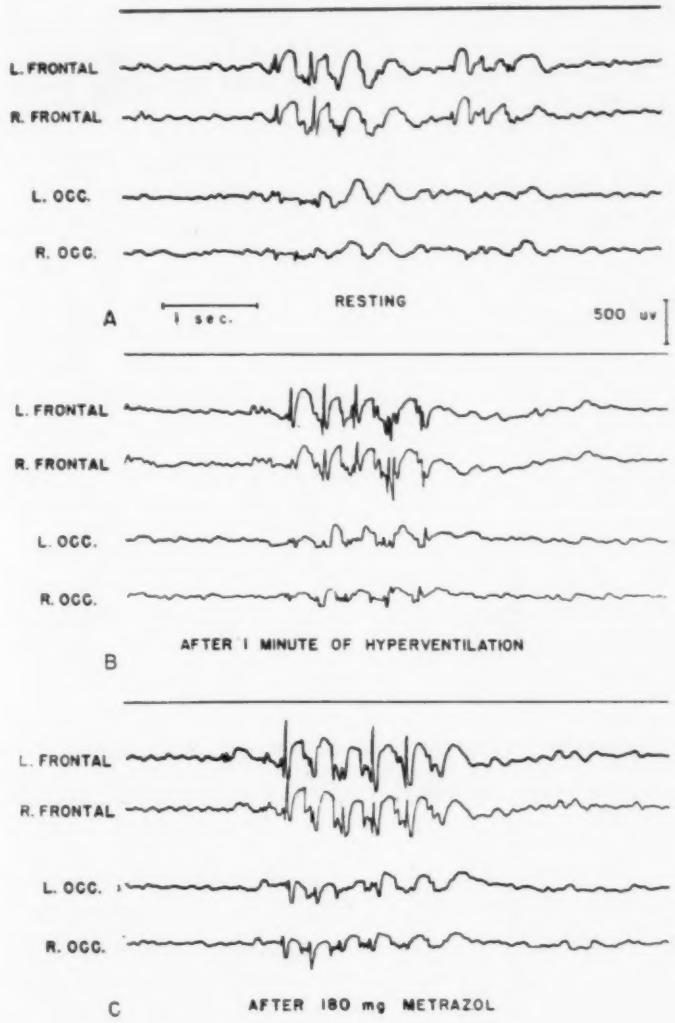


Fig. 4

Fig. 4.—Effect of slow intravenous injection of 400 mg. of "metrazol" (2 per cent solution, given at a rate of 20 mg. every half-minute) in D. P., a youth aged 18 years, with a history of two recent major nonfocal seizures. Note the reproduction of wave form and increase in amplitude of the discharges.

and spike discharges appeared. All 3 of these patients were considered to have idiopathic epilepsy. There was no clinical response in 2 patients, whereas in 1 patient a typical myoclonic seizure was produced. Localized

epileptiform discharges appeared in 2 patients, both of whose clinical attacks were focal in character. The habitual aura was reproduced in each of these patients. The remaining 2 patients had an abrupt onset of multiple spike and irregular, slow wave activity, which marked the onset of major nonfocal convulsive seizures. One of the patients was considered to have idiopathic epilepsy, and the other had habitually a sensory onset, followed by a major seizure. One patient experienced the exact reproduction of his aura without apparent significant change in the electroencephalogram.

The remaining 6 patients showed no significant epileptiform activity in the electroencephalogram after administration of "metrazol." In 2 of these patients the spontaneous attacks occurred infrequently (at

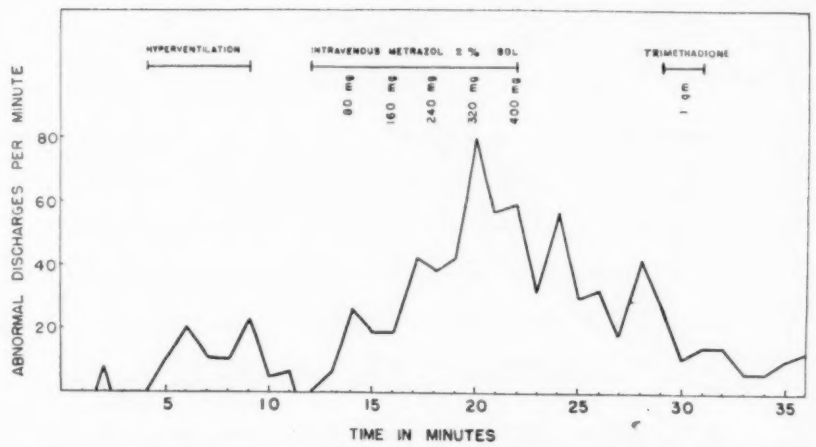


Fig. 5.—Graph illustrating the effect of hyperventilation, injection of "metrazol" and intravenous injection of trimethadione ("tridione") on the number of wave and spike discharges per minute in the patient whose electroencephalogram is shown in figure 4.

intervals of more than six months), and for 2 others the injections were discontinued after 100 and 240 mg., respectively, had been given because of the appearance of generalized muscular fasciculations, which were considered at the time to be an undesirable side effect. For another patient the injections were discontinued through an error after only 100 mg. had been given.

This group, with normal or borderline normal electroencephalograms, represents patients for whom some form of activation is most needed from a diagnostic standpoint. These preliminary results indicate that in about one-half such patients characteristic epileptiform discharges may be produced by this method. Furthermore, the type of electroencephalographic disturbance obtained was in general consistent with the clinical impression of the type of epilepsy. Also, in about one-half these

patients, "metrazol" induced minor or major clinical seizures which were similar to the habitual attacks.

Correlation with Type of Clinical Seizure.—As indicated in table 2, patients with idiopathic epilepsy are especially susceptible to the slow intravenous administration of "metrazol," as shown by electroencephalographic activation in 100 per cent of the 16 patients whose seizures were so diagnosed clinically. Of the other two groups of epileptic patients considered in this table, the majority of whom had symptomatic epilepsy, electroencephalographic activation occurred in about 70 per cent, with a somewhat larger average dose of "metrazol."

The discrepancy between electroencephalographic and the clinical activation in the idiopathic group (100 and 56 per cent, respectively) may represent the difficulty in detecting the slight clinical manifestations which may accompany short bursts of wave and spike discharge in the electroencephalogram. In contrast with this group, patients with seizures of focal cortical onset nearly all showed some clinical sign of the onset of a seizure when activation of focal discharge in the electroencephalogram was present.

Nonepileptic (Control) Subjects (31 Subjects).[19]— With the same method of administration (40 mg. per minute), the maximum dose of 400 mg. was given to 29 of the control subjects, the other 2 receiving 340 and 220 mg., respectively. Thirty of the 31 nonepileptic (control) subjects had no clinical manifestation of an epileptiform nature (table 1). The single exception was a schizophrenic patient who had had electroshock therapy but no history of spontaneous seizures. In this patient the pre-"metrazol" electroencephalogram was obscured by muscle artefact, and after injection of the drug there were paroxysmal bifrontal 4 to 5 per second, high voltage, rhythmic waves, which were increased with hyperventilation and were followed after a few minutes by a generalized convulsive seizure.

No significant alterations were produced in the electroencephalogram by "metrazol" in 23 of the 31 control subjects (74 per cent). Seven subjects had paroxysmal electroencephalographic disturbances induced without clinical manifestations of an epileptiform character. Three of these patients had paroxysmal abnormality in their pre-"metrazol" electroencephalogram, being of focal character for 1 and diffuse for the other 2. These patients were schizophrenic, 1 having had electroshock therapy nine months before. For the remaining 4 patients the pre-"metrazol" records were considered within normal or borderline normal limits. With "metrazol," 1 of these patients had short bursts of moderate

19. Twenty-seven of the nonepileptic (control) subjects were obtained through the cooperation of Drs. Read and Skitch, of the Verdun Protestant Hospital, Montreal.

voltage, 6 per second activity; 2 patients had more prolonged bursts of 3 to 6 per second bifrontal activity, and in 1 patient, with a history of seizures during insulin shock therapy, 2 per second, sharp and slow wave discharges were produced.

In summary, of the 27 control subjects who had normal or borderline normal pre-"metrazol" electroencephalographic records, paroxysmal electroencephalographic disturbances were induced in only 4 (15 per cent), none of whom showed any clinical epileptiform manifestations. In the other control subjects, "metrazol" produced only a slight increase

TABLE 3.—*Correlation of Results of "Metrazol" Injection with Frequency of Seizures, Medication, Age and Sex in 75 Patients Receiving "Metrazol" by Intramuscular or Slow Intravenous Route*

Frequency of Seizures	No. of Patients	Activation	
		Electroencephalographic	Clinical
1 or more per mo.	41	34 (83%)	26 (63%)
1 to 5 in 6 mo.	21	16 (76%)	8 (39%)
Less than 1 in 6 mo.	13	7 (54%)	5 (38%)
Anticonvulsant medication			
No medication	55	44 (80%)	26 (47%)
With medication	20	13 (65%)	12 (52%)
Age,			
4-19	25	21 (84%)	12 (48%)
20-29	26	20 (77%)	15 (57%)
30-39	14	12 (86%)	10 (71%)
40-55	10	4 (40%)	3 (30%)
Sex			
Male	44	34 (77%)	22 (50%)
Female	31	23 (74%)	17 (55%)

in frequency of the alpha rhythm and an increase in low voltage, rapid activity.

NONSPECIFIC SIDE EFFECTS OF "METRAZOL"

Certain nonspecific symptoms were induced with subconvulsive doses of "metrazol" in both the epileptic patients and the nonepileptic (control) subjects. These were most clearly seen with the slow intravenous administration, which allowed sufficient time for such effects to be noted. These symptoms are of importance, since they might well be confused with the aura of an epileptic attack.

A severe burning pain was caused by the intramuscular and by the intravenous injection of a 10 per cent solution, but this was clearly due to the irritative action of the drug and was not observed with intra-

venous injections of more dilute solutions (2 to 5 per cent). The first symptom experienced with the dilute solutions was often a disagreeable acrid odor described as a "bad smell." This was followed in some instances by vertigo and vague paresthesias ("tingling sensations"). Other general symptoms included apprehension, anxiety, general excitement, nausea and pallor, and in a few instances vomiting occurred. In 2 subjects, generalied muscular fasciculations followed relatively small nonconvulsive doses.

SUSCEPTIBILITY TO "METRAZOL" IN RELATION TO FREQUENCY OF SEIZURES, MEDICATION, AGE AND SEX

Other factors which may have affected the susceptibility of individual epileptic patients to "metrazol" are considered. The results obtained for patients receiving metrazol by the intramuscular or the slow intravenous method are summarized in table 3.

Frequency of Seizures.—These 75 patients were divided into three groups according to the average frequency of seizures: (*a*) patients with seizures more frequent than one per month, (*b*) patients with one to five attacks in six months and (*c*) patients with attacks occurring less frequently than one in six months. If the frequency of attacks was related to the seizure threshold, one might expect patients with very frequent attacks to be more susceptible to minimal doses of "metrazol." That this was the case was evident from the larger percentage of positive responses, both electrencephalographic and clinical, in the group with the most frequent seizures (83 and 63 per cent, respectively), as compared with the group with the least frequent seizures (54 and 38 per cent).

It may be of significance that 7 of the 13 patients with very infrequent seizures showed no evidence of epileptiform activity in the pre-"metrazol" electroencephalograms, and for 5 of these 7 subjects we were unable to produce any significant change in the electroencephalograms with "metrazol." It appears, therefore, that susceptibilty to "metrazol" may have some relation to seizure threshold.

Medication.—Epileptiform discharges were less frequently induced in the 20 epileptic patients receiving phenobarbital and/or diphenylhydantoin medication at the time of examination. Electroencephalographic activation occurred in only 65 per cent of these patients, as compared with 80 per cent of the 55 patients who were receiving no medication or for whom medication had been discontinued twenty-four hours or more prior to the examination. There was little difference in the percentage of clinical responses to "metrazol" in the group of patients who were examined while receiving medication as compared with the group who were not receiving medication. This was probably be-

cause the amount of "metrazol" given was limited more frequently by adequate electroencephalographic activation and the injections were usually discontinued, in an effort to produce a clinical response.

Age.—It appears from table 3 that patients over 40 years of age are less sensitive to "metrazol" than those in the younger age groups. One-half the subjects who failed to respond to "metrazol" also had infrequent spontaneous seizures, and/or normal electroencephalograms. This is apparently related to the increased convulsive threshold which seems to occur in patients above 40 years of age, as noted by Golla, Graham and Walter[20] and by Gibbs, Gibbs and Lennox.[21]

Sex.—There was no significant difference in the response of male and of female patients.

ACTIVATION OF EXPERIMENTAL FOCAL EPILEPOGENIC LESIONS IN MONKEYS

In order to test further the action of "metrazol" on focal epileptogenic lesions, the drug was administered to 7 monkeys (Macaca mulatta) in which such lesions had been experimentally produced by the application of alumina cream (a suspension of aluminum hydroxide in water) to the motor cortex, according to the method of Kopeloff, Barrera and Kopeloff.[22] With the initial advice of these authors, the monkeys used in this study were prepared by Dr. Alfred Pope and Dr. A. A. Morris for another series of investigations. The latter allowed us to study the responses of these animals to "metrazol." The alumina cream applied beneath a linen disk to the surface of the motor cortex produced chronic lesions, which had the local electroencephalographic features (random spikes) characteristic of the focal epileptogenic lesions of the human cortex. After about three months the animals began to have chronic recurring jacksonian seizures, which later progressed to become generalized attacks, but always with focal onset. The seizures appeared spontaneously or were induced by excitement.

All the 7 monkeys studied showed some random spike discharge periodically from the vicinity of the lesion produced by the alumina cream. Conducted disturbances were recorded from the homologous area of the opposite hemisphere. Five animals were having spontaneous

20. Golla, F.; Graham, S., and Walter, W. G.: Electroencephalogram in Epilepsy, J. Ment. Sc. **83**:137-155, 1937.

21. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch. Neurol. & Psychiat. **50**:111-128 (Aug.) 1943.

22. Kopeloff, L. M.; Barrera, S. E., and Kopeloff, N.: Recurrent Convulsive Seizures in Animals Produced by Immunologic and Chemical Means, Am. J. Psychiat. **98**:881-902, 1942.

jacksonian seizures at the time of the "metrazol" test. "Metrazol" was injected intramuscularly in doses of 10 to 16 mg. per kilogram of body weight.

About five minutes after the injection of "metrazol" there occurred an increase in the localized spike discharge from the region of the lesion. In 5 animals this was followed by a convulsive seizure of jacksonian onset almost identical with that of the animal's spontaneous attacks without "metrazol." In 3 of the animals the attack progressed, however, to a

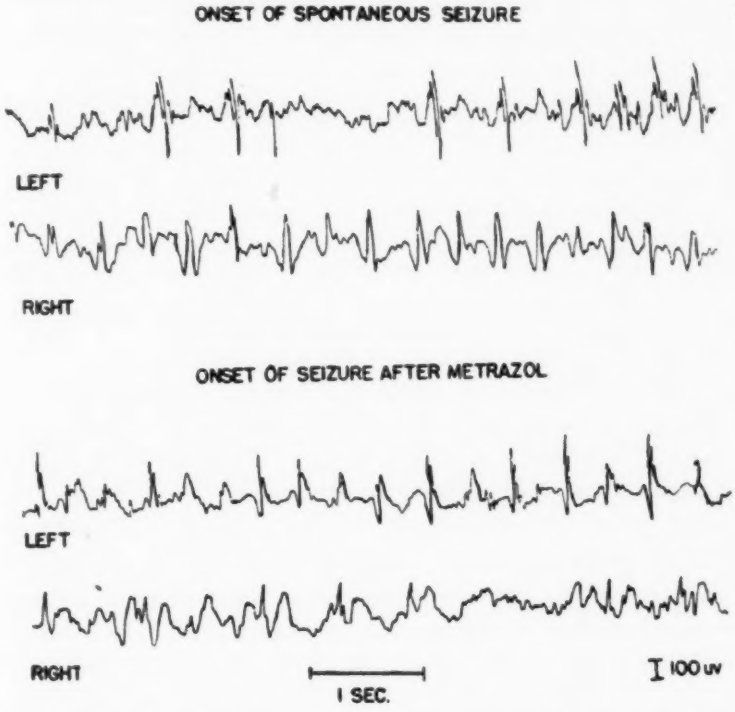


Fig. 6.—Electroencephalograms from an unanesthetized Macaca mulatta monkey four months after the instillation of alumina cream (aluminum hydoxide) over the left motor cortex. Note the similarity of pattern during the onset of the spontaneous seizure and that of the seizure induced with "metrazol." Spike discharges arose from the region of the lesion, and temporally dispersed, sharp waves were recorded from the opposite hemisphere with both types of seizures.

severer generalized seizure than was usually observed in these animals' spontaneous attacks. In 1 animal the dose happened to be just sufficient to produce only a minor, abortive jacksonian attack, without progression to a generalized attack. This was identical with his spontaneous attacks.

One animal was of particular interest, since "metrazol" was administered in a relatively large dose (20 mg. per kilogram) one month after placement of the alumina disk, before any spontaneous attacks had oc-

curred. At this time there was a slight increase in the electroencephalographic abnormality, but no convulsive seizure occurred. One month later, at which time no spontaneous attacks had yet occurred, "metrazol" was again administered intramuscularly at only one-half the previous dose (10 mg. per kilogram). On this occasion there was a much greater initial activation of local spike discharges in the electroencephalogram, followed by a convulsive seizure of jacksonian onset. The animal was subsequently seen to have many spontaneous jacksonian seizures of the same form. In another animal, in which an alumina cream pellet had been implanted in the motor cortex, no spontaneous seizures occurred during eight months' observation, but activation of the cortical focus and a jacksonian seizure could be induced with "metrazol."

The electroencephalograms taken during the "metrazol" seizures resembled those of the spontaneous attacks very closely (fig. 6), except that in some instances the rapidity of spread, both to adjacent cortical areas and to the contralateral cortex, was more rapid and more extensive with "metrazol" than it was in the spontaneous attacks observed and recorded.

It is felt that if the slow intravenous method had been used with the monkeys, giving a better control of the rate and amount of "metrazol" injected, the character and severity of the spontaneous seizures could have been reproduced more closely than they were with the intramuscular method. However, the facts that in all instances the seizures were of jacksonian onset, were similar to the spontaneous attacks and began at the site of the lesion produced by the alumina cream are sufficient proof that experimental local epileptogenic lesions of this type are sensitive to "metrazol." Effective doses two to three times as large were required to produce convulsions in 14 normal monkeys whose seizure thresholds were being studied for another series of experiments.

COMMENT

It is clear from the preceding results that the slow intravenous injection of "metrazol" is the method of choice for the activation of a patient's habitual or characteristic pattern of epilepsy, as judged either by the electroencephalogram or by the manner of onset of the clinical seizure.[23] With this method, the concentration of the drug in the brain

23. Since this manuscript was submitted for publication, there has appeared in the November 1947 issue of the ARCHIVES, page 533, an important contribution by Kaufman, Marshall and Walker, entitled "Activated Electroencephalography." Only patients with post-traumatic epilepsy were studied, but in about 44 per cent of 97 patients "metrazol" provided a satisfactory activation of focal discharge in the electroencephalogram. Of the several methods employed, administration of "metrazol" was considered to be the most satisfactory, when rapid intravenous in-

is gradually built up, with the result that a predisposed area becomes activated before the entire brain is "seized" by a generalized epileptic discharge. When large doses are given by rapid intravenous injection, this generalized discharge occurs so rapidly that there is no time for selective activation of an habitual epileptic process. Undoubtedly, the spread of epileptic discharge from an activated focus is also facilitated by the action of "metrazol" on the entire brain. With the proper rate of administration, however, "metrazol" may simply aid in the "self facilitation" which characterizes the epileptic process once it has begun. This suggests that investigation of the mode of action of "metrazol" might shed light on the mechanism of spontaneous seizures in epileptic patients.

Unfortunately, little is known concerning the fundamental physicochemical action of "metrazol" on the brain which might explain its convulsant properties. Results have been contradictory in regard to the effect of "metrazol" on cerebral blood flow and oxygen metabolism.

For example, Hall[24] reported a striking decrease in blood flow in the carotid artery and the meningeal branch of the jugular vein in the rabbit with the onset of a "metrazol" convulsion, while Forbes and Nason,[25] by observation of cerebral vessels through a window in the skull, did not find constant vasoconstrictor effect, but more often noted vasodilatation. Jasper and Erickson,[26] studying focal cerebral blood flow, hydrogen ion concentration and electrical discharges following the injection of "metrazol" in the cat, concluded that the increased blood flow

jection (200 mg.) was used. We have since modified our technic for routine use, owing to the number of epileptic patients who are resistant to "metrazol" when administered at the slow intravenous rate (40 mg. per minute) recommended in this report. An attempt to adjust the dosage to body weight should also be made. We are now beginning with a rapid initial dose of 1 mg. per pound (2.2 mg. per kilogram) of body weight, which is followed in thirty seconds by another dose of 0.5 mg. per pound (1.1 mg per kilogram) of body weight and successive doses of 0.5 mg. per pound, every thirty seconds, until adequate electroencephalographic activation is obtained, or, if desired, until a clinical seizure is produced. The maximum dose is usually limited to a total of 4 mg. per hundred pounds (45 Kg.). Even with this more rapid method and with large doses, certain patients seem remarkably resistant. With the large doses, "metrazol" seizures may be induced which have no significance relative to the patient's habitual seizures. Consequently, we are still in need of a more satisfactory method of activation. The use of sleep, natural or induced with barbiturates, has only a limited usefulness in our experience, and it is not effective for the controlled observation of the form of clinical seizures.

24. Hall, G. E.: Physiological Studies in Experimental Insulin and Metrazol Shock, Am. J. Psychiat. **95**:553-566, 1938.

25. Forbes, H. S., and Nason, G. I.: Effect of Metrazol on Cerebral Vessels, Proc. Soc. Exper. Biol. & Med. **43**:762-765, 1940.

26. Jasper, H. H., and Erickson, T. C.: Cerebral Blood Flow and p_H in Excessive Cortical Discharge Induced by Metrazol and Electrical Stimulation, J. Neurophysiol. **4**:333-347, 1941.

and changes in the p_H occurred as a result of the excessive cortical activity and were not related to the mechanism of the convulsant action of "metrazol."

In studies on the action of "metrazol" by direct recording of local oxygen tension in the cortex with a noble metal electrode, Davis, McCulloch and Roseman[27] reported an initial drop in oxygen tension before the onset of the electrical discharge. Recent studies with modifications of this technic by Davies and Remond[28] showed that the electrical discharge appears before the changes in oxygen tension. Therefore, as with the p_H and the blood flow, changes in oxygen tension seem to occur as a result of excessive cortical discharge and may not be related to the mechanism of "metrazol" action. In vitro studies by MacLeod and Reiss[29] and Elliott and Libet[30] failed to show any significant effect of "metrazol" on the rate of respiration of brain tissue at concentrations of the drug likely to be found in vivo.

The extreme rapidity of action of convulsant doses of "metrazol" when given by rapid intravenous injection is similar to the effect produced by electroshock. This suggests a direct action on the polarization or permeability of the nerve cell membranes, rather than an indirect action through changes in circulation of oxygen metabolism. This concept received some confirmation in the studies of Spiegel and Spiegel-Adolph[31] on changes in permeability of the brain, as determined by electrical impedance measurements during "metrazol" seizures in guinea pigs, and is in accord with the interpretation given by Goodwin, Kerr and Lawson[32] of their electrocorticographic studies on the action of "metrazol" on the cortex of the rabbit. It is of interest to recall, in this regard, the deductions made by McQuarrie, Manchester and Husted[33] from the results of care-

27. Davis, E. W.; McCulloch, W. S., and Roseman, E.: Rapid Changes in 0_2 Tension of Cerebral Cortex During Induced Convulsions, Am. J. Psychiat. **100**: 825-829, 1944.

28. Davies, P. W., and Remond, A.: Changes in the Oxygen Tension of the Cerebral Cortex of the Cat During Experimentally-Induced Convulsions, A. Research Nerv. & Ment. Dis., Proc., 1946, to be published.

29. MacLeod, L. D., and Reiss, M.: Brain Respiration and Glycolysis in Cardiazol Convulsions, J. Ment. Sc. **86**:276-280, 1940.

30. Elliott, K. A. C., and Libet, B.: Studies in the Metabolism of Brain Suspensions: I. Oxygen Uptake, J. Biol. Chem. **143**:227-246, 1942.

31. Spiegel, E. A., and Spiegel-Adolph, M.: Permeability Changes in the Brain Induced by Metrazol and Insulin Convulsions, J. Nerv. & Ment. Dis. **93**: 750-755, 1941.

32. Goodwin, J. E.; Kerr, W. K., and Lawson, F. L.: Bioelectric Responses in Metrazol and Insulin Shock, Am. J. Psychiat. **96**:1389-1405, 1940.

33. McQuarrie, I.; Manchester, R. C., and Husted, C. A.: A Study of Water and Mineral Balances in Epileptic Children, Am. J. Dis. Child. **43**:1519-1543 (June) 1932.

fully controlled hydration studies on epileptic patients, from which they postulated that an inherent defect in the mechanism for regulating permeability of nerve cells is characteristic of epilepsy.

Although the average epileptic patient is more susceptible to "metrazol" than is the average nonepileptic subject, this is not always true. Some epileptic patients seem resistent to large doses (800 mg. by slow intravenous injection in a recent patient) which would produce a seizure in an occasional subject who had no previous history of epilepsy. "Metrazol" must be used with caution, therefore, as an aid to the differential diagnosis of epilepsy, in contrast with other conditions, such as hysteria or syncope.

It should be emphasized that only the induction of definite epileptiform patterns in the electroencephalogram, such as spikes, sharp waves or high voltage wave and spike sequences, can be considered definitely diagnostic of epilepsy. The appearance of minimal changes in the electroencephalogram, such as short bursts of 4 to 6 per second waves or other minor, nonspecific irregularities, must be interpreted with caution, since such changes may be observed with the same amount of "metrazol" in many nonepileptic subjects.[34]

These preliminary studies indicated that the optimum rate of administration of "metrazol" in 2 per cent solution was about 40 mg. per minute. It is probable that further studies may make it advisable to alter this rate for individual patients; for example, it might be better to use a slower rate for children or for patients with very frequent seizures or to increase this rate for older patients or for patients with few attacks. The amount of medication might also be an indication for altering the rate of administration and the maximum dose employed. It should be emphasized that the maximum dose employed is a function of the rate of administration; the more rapid the rate, the less the amount required to produce a given effect. Maximum doses given by the slow intravenous method cannot be directly compared with those given by rapid intravenous injection.

In our experience, the slow intravenous administration of "metrazol" is of greatest value for the analysis of the type of epilepsy in a given patient, particularly in the differentiation of idiopathic and symptomatic epilepsy in patients whose electroencephalogram is normal or equivocal or

34. After the completion of this study, investigations of a minimal electroencephalographic response to "metrazol" in epileptic and in control subjects was reported by Ziskind and Bercel (Studies in Convulsive Thresholds: II. Convulsive Threshold in Epileptics and Non-Epileptics, Tr. Am. Neurol. A., 1946, to be published) at the meeting of the American Neurological Association in June 1946, and the manuscript was provided by these authors. Their method, recently described in *Science* (104:462-463, 1946), is similar in some respects to the slow intravenous method used in our studies.

in those whose attacks are of uncertain form and have not been adequately observed. The facility with which the bilaterally synchronous wave and spike pattern is induced with relatively small doses of "metrazol" in patients with idiopathic epilepsy, and not in patients with symptomatic epilepsy, makes this test of critical value. Furthermore, the focal activation of a superficial epileptogenic lesion makes possible more extensive and accurate electroencephalographic study and permits the observation of the aura or onset of the seizure itself under controlled conditions.

There is another observation of theoretic interest which may be made from the data of these studies, namely, that patients with bilaterally synchronous electroencephalographic disturbances, either idiopathic or resulting from deep-seated epileptogenic lesions probably involving subcortical structures, are more susceptible to "metrazol" than patients with seizures which are of superficial cortical onset. This observation suggests not only that the onset of the petit mal discharge, for example, may also be in subcortical structures, as was previously suggested by Jasper and Kershman[13] and Penfield and Erickson,[35] but that subcortical regions of the brain may be more sensitive to activation by "metrazol."

SUMMARY AND CONCLUSIONS

Electroencephalographic and clinical responses to "metrazol" were studied in 132 epileptic patients and in 42 nonepileptic, control, subjects in the attempt to develop a method for the activation of epileptic discharge for diagnostic purposes. Three modes of administration of "metrazol" were studied in separate groups of patients: rapid intravenous injection, intramuscular injection and slow intravenous injection of a 2 per cent solution at the rate of 20 mg. each half-minute. Monkeys with experimentally produced focal epileptogenic lesions were also studied.

The method of rapid intravenous injection of small doses of the 10 per cent solution was discarded because of the abrupt onset of its convulsant action, making observations on the form of onset of the epileptic pattern difficult, and because of the difficulty in regulating the optimum dose required. Some generalized "metrazol seizures" were obtained in epileptic patients whose habitual attacks were of focal onset.

Intramuscular injection of a 10 per cent solution was more satisfactory as a method for the activation of the patient's habitual pattern of electroencephalographic disturbance and form of clinical seizure, but the injections were painful and the dosage was difficult to assess and to control.

35. Penfield and Erickson,[18] pp. 137-142, 210-215 and 470-471.

The slow intravenous injection of the dilute solution was not painful, produced a gradual activation of epileptiform disturbance in the electroencephalogram and often induced the aura or onset of the patient's habitual clinical seizure, at which time the injection could be stopped (and phenobarbital administered) before a severe generalized attack occurred. Major seizures did occur, however, in a few patients. The principal results may be summarized as follows:

1. Epileptiform discharge was increased or induced in the electroencephalogram of 80 per cent of the epileptic patients studied with the slow intravenous method. A clinical response revealing the nature of the onset of the patient's spontaneous attacks occurred in 56 per cent of these patients.

2. An epileptiform seizure occurred in only 1 (3 per cent) of the nonepileptic (control) subjects given the maximum dose of 400 mg. of "metrazol" in the same manner. Paroxysmal 4 to 6 per second, bilaterally synchronous slow wave disturbances occurred in the electroencephalograms of 26 per cent of the control subjects. There was some evidence that this response indicated a low convulsive threshold, but the effect was considered nonspecific with regard to the diagnosis of clinical epilepsy.

3. Susceptibility to "metrazol" seemed related to the patient's convulsive threshold, since it was decreased in patients with infrequent seizures and in those receiving anticonvulsant medication at the time of the examination. Patients over 40 years of age seemed less susceptible.

4. Patients with idiopathic epilepsy, especially with a bilaterally synchronous wave and spike electroencephalographic pattern, were most sensitive to "metrazol." Patients with bilaterally synchronous electroencephalographic disturbances were more sensitive than those with superficial focal epileptogenic lesions of the cortex.

5. "Metrazol" slowly administered in small doses served to activate experimentally produced focal epileptogenic lesions of the cortex in monkeys and to induce seizures of focal motor onset.

6. The slow intravenous injection of dilute solutions of "metrazol" has definite advantages over other methods now available for the induction of seizures in epileptic patients. When used in conjunction with the electroencephalograph, it makes possible a clear diagnosis in many cases in which the nature of the seizures has previously been obscure.

Montreal Neurological Institute.

ROLE OF AFFERENT IMPULSES IN EXPERIMENTAL CONVULSIONS

E. GELLHORN, M.D., Ph.D.
AND
H. M. BALLIN, Ph.D.
MINNEAPOLIS

ALTHOUGH clinical evidence on the effect of afferent impulses in either precipitating or preventing epileptic attacks has been presented since the time of Hughlings Jackson[1] (for more recent studies see Holmes,[2] Thomas[3] and Walshe[4]), little experimental work has been done which throws light on the mechanisms involved. Franck[5] stated that stimulation of the occipital cortex may produce convulsive activity after the motor cortex has been sensitized through a previous stimulus which induced a convulsive seizure. These impulses seem to act on the motor cortex, since extirpation of the ipsilateral motor area prevents this effect (Rosenbach and Danillo[6]). Franck stated also that stimulation of sensory nerves may precipitate seizures. Amantea[7] observed that movements can be evoked in dogs after a receptive zone in the sensorimotor cortex has been strychninized. Furthermore, he claimed that in "hypersensitive" dogs such stimuli may produce generalized convulsions. More recently, Adrian

This study was aided by a grant of the United States Navy, Office of Research.

From the Laboratory of Neurophysiology, Department of Physiology, University of Minnesota.

1. Taylor, J.; Holmes, G., and Walshe, F.M.R.: Selected Writings of John Hughlings Jackson, London, Hodder & Stoughton, Ltd., 1931.

2. Holmes, G.: Local Epilepsy, Lancet **1**:957-962, 1927.

3. Thomas, A.; Menuau and de Ajuriaguerra: Crises d'épilepsie tonique spontanées ou provoquées chez malades atteints d'une affection organique des centres nerveaux, Rev. neurol. **74**:171-172, 1942.

4. Walshe, F.M.R.: On the Mode of Representation of Movements in the Motor Cortex, with Special Reference to "Convulsions Beginning Unilaterally," Brain **66**:104-136, 1943.

5. Franck, F.: Fonctions motrices du cerveau, Paris, 1887.

6. Rosenbach, and Danillo, cited by Luciani, L.: Human Physiology, London, Macmillan & Co., Ltd., 1911-1921.

7. Amantea, G.: Ueber experimentelle beim Versuchstier infolge afferenter Reize erzeugte Epilepsie, Arch. f. d. ges. Physiol. **188**:287-297, 1921.

and Moruzzi[7a] showed that an increase in the frequency of discharges originating in the convulsant cortex occurred in pyramidal fibers as the result of afferent stimulation.

One finds likewise reference to emotion as one of the factors possibly involved in the precipitation of a convulsive attack in man, although no experimental work seems to have been done on this problem.

It was therefore decided to study the effect of afferent impulses on picrotoxinized cats in order to determine whether these factors are able to precipitate convulsions or to increase the intensity of convulsions which have been induced prior to stimulation. Electrical or mechanical stimulation of the sciatic nerve was used; in addition, the effect of stimulation of the hypothalamus was studied, since this area is known to be involved in emotional processes. The simultaneous study of cortical and hypothalamic potentials was undertaken in an attempt to throw light on the mechanisms involved.

PRESENT STUDY

Method.—The experiments were performed on more than 40 cats, most of which were anesthetized with a solution of 5, 5-diallylbarbituric acid and urethane[8] ("dial with urethane"), 0.45 cc. per kilogram of body weight injected intraperitoneally. Cortical and hypothalamic potentials were recorded with monopolar or bipolar silver electrodes through a four channel Offner crystograph after adequate amplification. The cortical areas included motor, sensory projection and suppressor areas. Clips were inserted into the skin of the foreleg and hindleg, and the potentials resulting from movement were amplified and recorded. The Goodwin stimulator, supplying condenser discharges, was used at appropriate voltages, mentioned in the individual experiments. The frequency of stimulation was 90 per second unless stated otherwise. Picrotoxin was injected intravenously slowly in quantities of 0.1 and 0.2 mg., and the effect of afferent impulses elicited by stimulation of the sciatic nerve or the hypothalamus was studied at various levels of pictrotoxinization. In a series of animals the development of convulsions and the influence of afferent stimuli on cortical potentials were studied after the intravenous injection of "intocostrin".[9]

The posterior portion of the hypothalamus was stimulated with condenser discharges at an intensity adequate to elicit a distinct or maximal contraction of the nictitating membrane and dilation of the pupil. No skeletal movements were seen from the stimulation under control conditions. Stimulation of the sciatic nerve either electrically (by condenser discharges) or mechanically (by ligation of this nerve) resulted in pupillary dilatation and increased rate of respiration.

Results.—At various levels of picrotoxin poisoning, accomplished by intravenous injection of this drug, either the hypothalamus or the sciatic

---

7a. Adrian, E. D., and Moruzzi, G.: Impulses in the Pyramidal Tract, J. Physiol. **97**:153-199, 1939.

8. Each cubic centimeter contains 1 Gm. "dial," 0.1 Gm. urethane and 0.4 Gm. monoethylurea.

9. "Dial" and "intocostrin" (a preparation containing therapeutically desirable products of raw curare) were supplied by Ciba Pharmaceutical Products, Inc., and E. R. Squibb & Sons, respectively.

nerve was stimulated, and the effect was studied with regard to convulsive movements and to brain potentials. In numerous instances such stimulation caused transient convulsive movements. This precipitation of convulsive movements was not confined to the period of the stimulation but continued for various lengths of time afterward. The duration of the effect was apparently related to the strength of the stimulation and was greatest when ligation of the sciatic nerve was employed. The level of picrotoxin poisoning at which this phenomenon occurred varied widely in different animals, although the methods of anesthetization were uniform. By repeating the injections of picrotoxin at suitable intervals, it was possible to show several times in the same animal that convulsions may be precipitated by sciatic or hypothalamic stimulation. When these

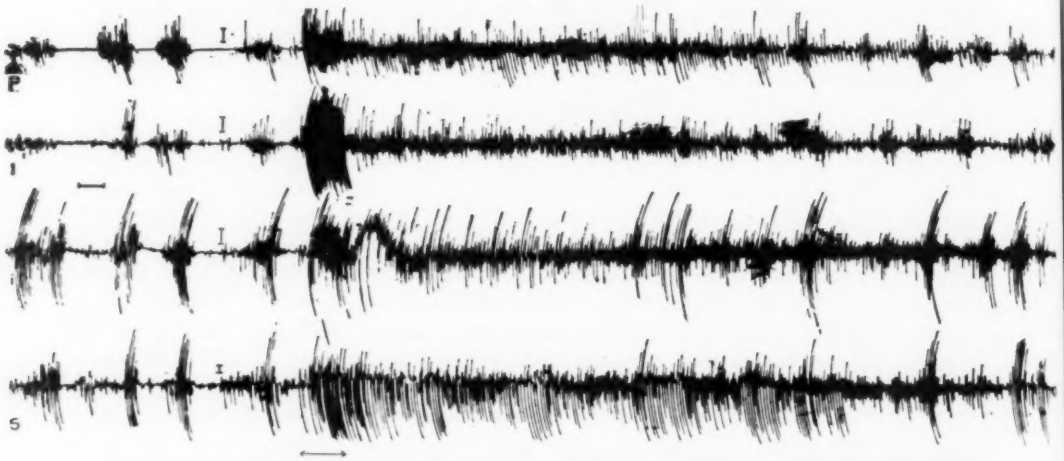


Fig. 1.—Effect of stimulation (↔) of the contralateral posterior hypothalamus (4.8 volts for three seconds) on the motor cortex (*5*), the parietal (*i*), the posterior suppressor area (*p*) and the auditory projection area (*1*). The horizontal line in all tracings represents two seconds; the vertical line, 100 microvolts. Picrotoxin, 0.3 mg. per kilogram, was given intravenously.

effects occur at high degrees of picrotoxinization, they may be accompanied with tonic-clonic convulsions showing large, rapid potentials, comparable to those seen in cases of status epilepticus.

Figure 1 shows in a typical experiment the change in cortical potentials which accompanies the onset of convulsions precipitated by the stimulus. Whereas prior to stimulation the potentials are grouped, a continuous rapid spike activity follows stimulation of the hypothalamus. The greater frequency of discharge is similar to that described earlier (Morison, Finley and Lothrop[10]; Murphy and Gellhorn[11]), in experiments on anesthe-

10. Morison, R. S.; Finley, K. H., and Lothrop, G. N.: Influence of Basal Forebrain Areas on the Electrocorticogram, Am. J. Physiol. **139**:410-416, 1943.

11. Murphy, J. P., and Gellhorn, E.: The Influence of Hypothalamic Stimulation on Cortically Induced Movements and on Action Potentials of the Cortex, J. Neurophysiol. **8**:341-364, 1945.

tized cats not given injections of convulsant drugs, except for the greater magnitude of the potentials. Figure 1 serves also to illustrate that the excitatory effect is not restricted to the motor cortex but is likewise present in sensory projection and suppressor areas, as was to be expected from previous studies (Gellhorn[12]). When calibration in this figure is taken into account, it is seen that the spikes of the motor area are larger than those of other areas. However, as will be pointed out later, this was by no means the rule.

Figure 2 shows the effect of stimulation of the hypothalamus on the cortex and on the contralateral hypothalamus of a cat in which, owing to the administration of picrotoxin, slight convulsions were present prior to stimulation. At this time the cortex showed large spikes appearing in

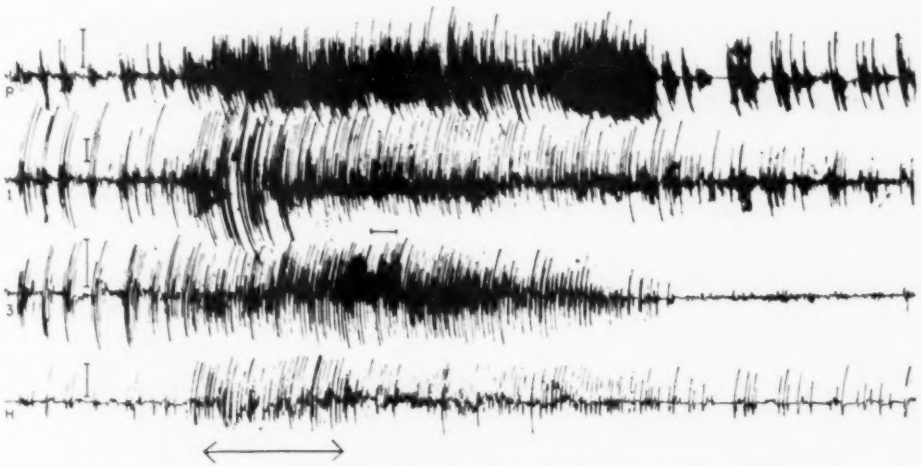


Fig. 2.—Effect of stimulation (↔) of the contralateral hypothalamus (1.9 volts for ten seconds) on the posterior suppressor (*p*), auditory projection (*1*) and motor (*3*) areas and the posterior hypothalamus (*H*). Calibration: 100 microvolts; 0.2 mg. of picrotoxin per kilogram injected intravenously.

the form of grouped "dial" potentials, whereas single spikes appeared in the hypothalamogram. Very weak stimulation of the hypothalamus greatly aggravated the convulsions and increased the frequency of spike potentials in all leads. The first and fourth records show a return to prestimulatory conditions about thirty seconds after stimulation ceased, whereas the other records show a depression of electrical activity, such as commonly occurs after convulsive discharges (Strauss and Rahm,[13] Gellhorn and Ballin[14]). The great effectiveness of this mild hypothala-

12. Gellhorn, E.: The Effect of Afferent Impulses on Cortical Suppressor Areas, J. Neurophysiol. **10**:125-132, 1947.

13. Strauss, H., and Rahm, W. E., Jr.: Reactions of the Electroencephalogram and Metrazol Injections, Proc. Soc. Exper. Biol. & Med. **40**:1-2, 1939.

14. Gellhorn, E., and Ballin, H. M.: Water Intoxication and the Electroencephalogram, Am. J. Physiol. **146**:559-566, 1946.

mic stimulation, which was accompanied with maximal dilatation of the pupil and maximal contraction of the nictitating membrane, appears to be due to the fact that this experiment was performed twenty-four hours after "dial" medication. It is worthy of note that in this experiment, as in many others, the effect on the posterior suppressor areas was particularly pronounced.

The record reproduced in figure 3 was obtained from a cat on which operation was performed under ether anesthesia. Artificial respiration

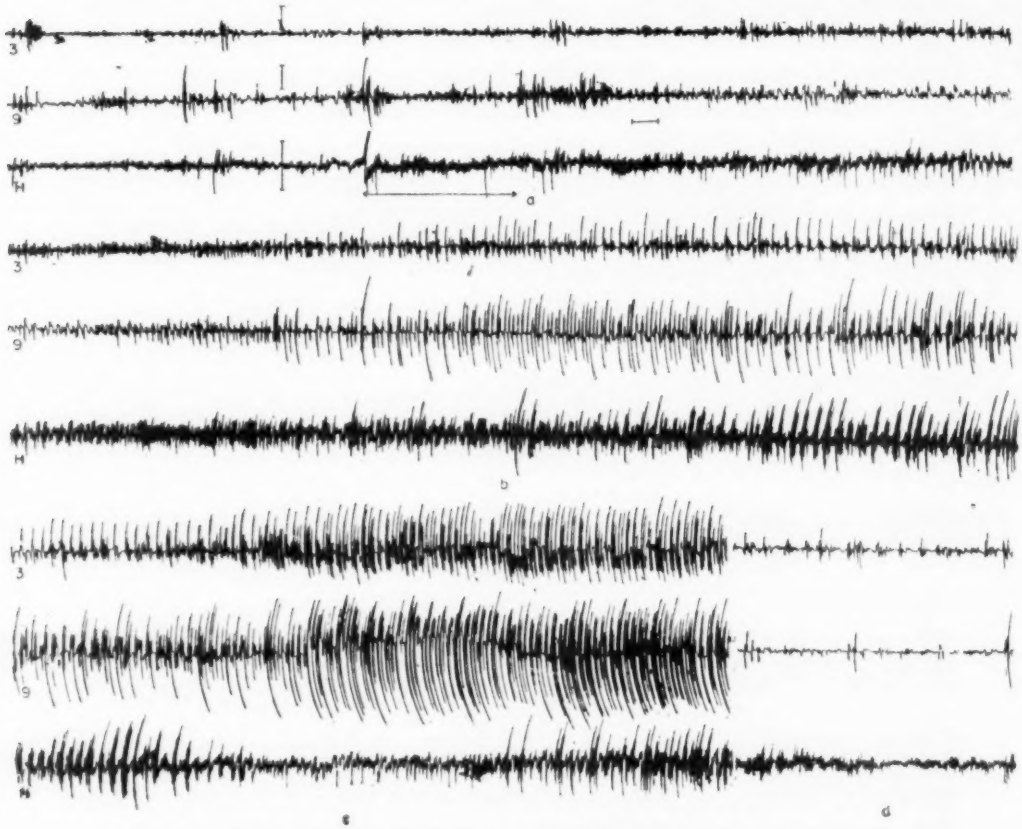


Fig. 3.—Effect of stimulation of the contralateral sciatic (↤↦) nerve with 1.9 volts for five seconds on the motor area (*3*), the optical projection area (*9*) and the posterior hypothalamus (*H*) of an etherized cat, which had been given "intocostrin." Records *a* to *c* are continuous.

was administered and "intocostrin" was injected. The potentials seen under control conditions are small and frequent and show occasional small spikes. During stimulation of the sciatic nerve with a weak current (1.9 volts) the potentials remain essentially unchanged, but after cessation of stimulation they increase gradually. At first the "background" potentials increase in amplitude, and only infrequently do spikes appear, which are most distinct in the hypothalamus (end of record *a*). Then (record *b*)

spikes increase in size and finally in frequency (record *c*). Grouping of spikes is most prominent in the record from the hypothalamus, but the cortical records reveal multiple spikes likewise. Although the progression of convulsions is similar in the various cortical and subcortical areas,

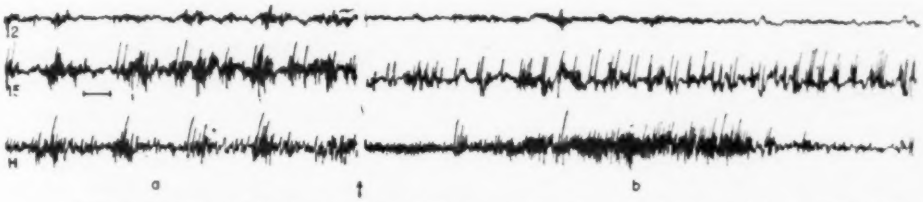


Fig. 4.—Effect of stimulation of the posterior hypothalamus with 7 volts for ten seconds (at the arrow) on the suprasylvian gyrus (*12*), the gyrus proreus (*15*) and the posterior hypothalamus (*H*). Records *a* were taken before, and records *b* fifteen seconds after, stimulation. Pictrotoxin, 0.2 mg. per kilogram, was given intravenously.

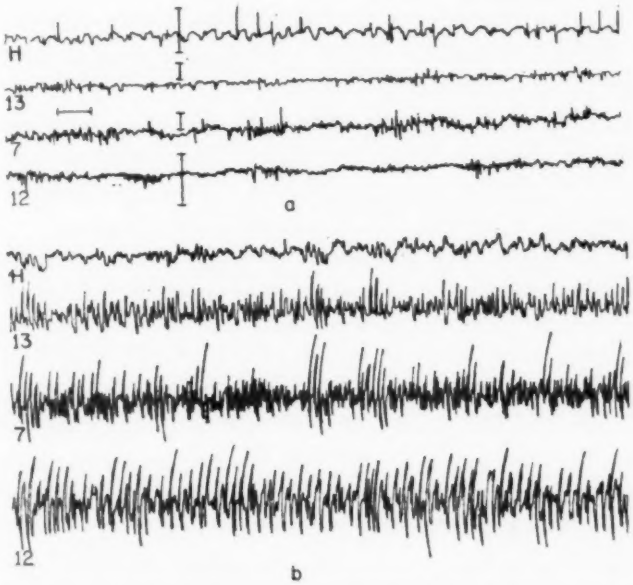


Fig. 5.—Effect of stimulation of the posterior hypothalamus (11 volts for ten seconds) on the posterior hypothalamus (*H*), the posterior sigmoid gyrus (*13*), the gyrus proreus (*7*) and the gyrus suprasylvius (*12*) of a cat under "dial" anesthesia given "intocostrin" the previous day. Calibration: 50 microvolts. Records *a* were taken before, and records *b* ninety seconds after, stimulation.

differences are not without interest. Thus, it is noted that the maximal activity of the hypothalamus does not coincide with that of the cortex but precedes it (beginning of record *c*). Furthermore, the "convulsive" activity in a sensory area (optic projection) is severer than in the motor cortex. The complete reversibility of the effect is shown at the end of record *d*, which was obtained after an interval of two minutes.

A similar lack of parallelism between hypothalamic and cortical potentials was also seen in experiments in which convulsions were precipitated or aggravated by hypothalamic stimulation. Figure 4 shows that about thirty seconds after hypothalamic stimulation "convulsive" activity is recorded from the hypothalamus for a short period. However, this alteration in hypothalamic activity does not show any repercussions in the cortex, since "convulsive" spikes continue at the same rate and amplitude in the gyrus proreus and the small potentials recorded from the suprasylvian gyrus show only slightly increased frequency during this "convulsive" outburst. The record of figure 5 is particularly instructive, since it shows that "convulsive" spikes develop in various cortical areas whereas the hypothalamic potentials remain small. Here, again, stimulation of the hypothalamus induced these effects. The data suggest that although the hypothalamus may initiate convulsions, it is not responsible for maintaining this activity nor does it control the rate and intensity under the specific conditions of our experiments.

Although the problem of the relative sensitivity of various cortical areas to convulsant stimuli will be investigated later, it may be stated that no preferential sensitivity of the motor cortex to picrotoxin could be found. Records such as those illustrated in figure 1, in which convulsive potentials were larger in the motor than in the sensory areas, were in the minority. It was observed frequently that the parietal lobe showed large spikes under the influence of picrotoxin when the electrogram of the motor area showed potentials of only slightly increased amplitude. Furthermore, it was found that hypothalamic or sciatic stimulation induced severe "convulsive" activity in the sensory cortex, whereas the potentials of the motor area were increased only to a slight extent. In agreement with these findings, it was seen in many experiments that under lighter picrotoxinization electrograms of sensory projection and/or suppressor areas showed ample evidence of "convulsive" activity, although actual convulsive movements were absent. This was true whether or not the sciatic nerve or the hypothalamus was stimulated.

A closer study of the changes in the action potentials shows that in the picrotoxinized brain hypothalamic or sciatic stimulation is followed by different types of reactions which are related to the changes seen in the normal cortex as the result of afferent stimulation (Gellhorn and Ballin[15] and the older work cited in this paper). These authors concluded that weak afferent stimuli cause disappearance of "dial" potentials without significant changes in background activity. On stronger excitation the background potentials show a greater frequency of discharge than those appearing between the groups of "dial" potentials prior to

15. Gellhorn, E., and Ballin, H. M.: The Effect of Afferent Impulses on Hypothalamic Potentials, Am. J. Physiol. **146**:630-635, 1946.

stimulation. Finally, the highest degree of excitation is characterized by an increase in frequency and amplitude of the background potentials. In all three conditions the grouped "dial" potentials are absent as a result of afferent stimulation. It was suggested in the earlier investigation that these effects indicate a lessened degree of synchrony of the discharging neurons and, with an increasing degree of stimulation, additional recruit-

Fig. 6.—Effect of ligation of the contralateral sciatic (↛) on the gyrus suprasylvius (*12*), the posterior sigmoid gyrus (*15*) and the motor area (*5*) in a picrotoxinized cat. Calibration: 300 microvolts.

ment of previously inactive nerve cells. This scheme is suitable for the interpretation of the changes in potentials seen in the present investigation. Apparently, afferent impulses arising from stimulation of the sciatic nerve or the hypothalamus cause asynchronization of potentials and recruitment of cortical neurons. This is clearly seen in figures 2, 3 and 5,

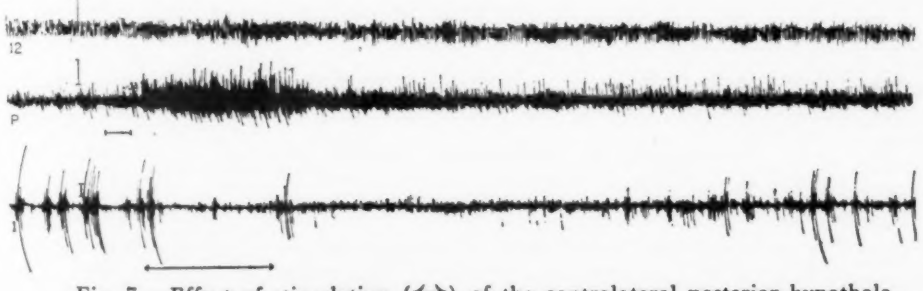


Fig. 7.—Effect of stimulation (↚↛) of the contralateral posterior hypothalamus (4.8 volts for ten seconds) on the auditory projection area (*1*), the posterior suppressor area (*p*) and sensory (suprasylvian) area (*12*) in a picrotoxinized cat. Calibration: 100 microvolts.

in which both frequency and amplitude of the potentials increase as the result of afferent stimulation. Even under these conditions different cortical areas may show significant differences. The greatest degree of recruitment takes place in the motor area (fig. 1), whereas in the experiment illustrated by figure 6 the opposite is true. In the latter experiment the recruitment seems to be least in the motor cortex, in which smaller, but

more frequent, potentials appear than were recorded prior to stimulation, whereas the electrocorticograms of the sensory areas suggest by the occurrence of frequent and large potentials that recruitment of additional neurons has taken place.

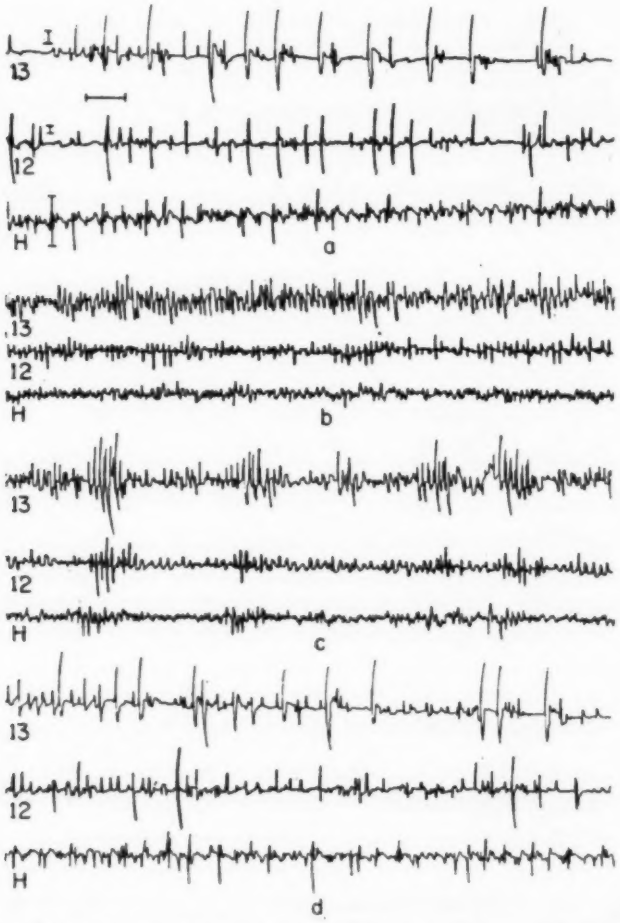


Fig. 8.—Effect of hypothalamic stimulation on the posterior sigmoid gyrus (*13*), the suprasylvian gyrus (*12*) and the hypothalamus (*H*) of a cat which had received injections of "dial" and picrotoxin thirty-six and twenty-four hours, respectively, prior to the experiment. The hypothalamus was stimulated (11 volts for ten seconds) between *a* and *b*. Records *c* and *d* were taken after intervals of about one minute. Calibration: 100 microvolts.

If it is true that spikes represent a maximal degree of synchronization of neurons and that mild afferent stimuli may induce a lesser degree of synchrony without additional recruitment, it is to be expected that such stimuli would cause a temporary disappearance of convulsive activity. This is indeed the case, in figure 7 (third line), in which "convulsive" potentials disappear completely during, and for some time after, stimula-

tion and are replaced by background activity of a degree similar to that seen in the control period.

Further examples of temporary suppression of spike activity after afferent stimulation are shown in figure 8. This figure illustrates well the relation of spike activity, synchrony and afferent stimulation which exists, for the various stages follow each other rather slowly in these experiments. Prior to hypothalamic stimulation the picrotoxinized cat showed spike potentials in cortex and hypothalamus (*a*). Immediately after stimulation the large spike potentials disappeared and were replaced by small, frequent background potentials (*b*). At a later stage (*c*) grouped "dial" potentials, which were separated from each other by small, and often

Effect of Hypothalamic Stimulation on Frequency of Cortical and Hypothalamic Potentials in a Picrotoxinized Cat*

Area	Potentials	Control	After Stimulation, Seconds			
			0-40	40-80	140-180	240
Post-cruciate gyrus	Spikes	35†	0	0	0	25
	"Dial" potentials	0	0	15	13	0
	Background‡ potentials	185	300	360	375	225
Supra-sylvian gyrus	Spikes	40	0	0	0	30
	"Dial" potentials	0	0	5	8	0
	Background potentials	190	370	300	360	210
Posterior hypothal-amus	Spikes	35	0	0	0	30
	"Dial" potentials	0	0	5	8	0
	Background potentials	300	340	390	420	340

*5.3 volts, frequency, 88 per second for ten seconds.
†Frequency per minute.
‡Potentials which in general have an amplitude of 100 microvolts or less.

frequent background potentials, were seen in their place. Finally, the "dial" potentials passed away, and the spikes returned (*d*). This experiment illustrates the principle that stimulation involves decreased synchrony and that during recovery the original state is attained through stages of increasing synchronization. A moderate degree of synchronization is indicated by the appearance of "dial" potentials, and a higher one, by spikes. The table (from an experiment performed on another cat) shows similar results and gives more detailed, quantitative data.

It was suggested earlier in the paper that the changes in cortical potentials described in these experiments are determined by the strength of afferent stimuli. In response to weak stimuli, a lessened degree of synchronization occurs in cortical potentials, whereas strong afferent

stimulation causes asynchronization and recruitment of previously non-discharging cells. This interpretation is borne out by experiments, such as that illustrated in figure 9, in which the effect of stimulation of the sciatic nerve with different intensities is recorded on a normal and on a

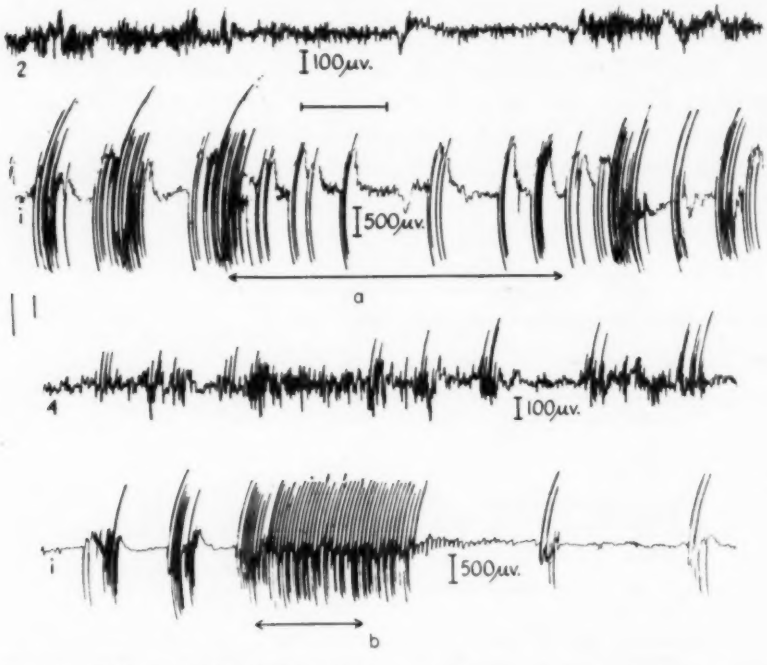


Fig. 9.—Effect of stimulation of the contralateral sciatic nerve on a strychninized suppressor (*i*) and a nonstrychninized sensory area (*2* and *4*). Records *a* were taken after stimulation (3.6 volts, 40.4 per second) for twenty seconds; records *b*, after stimulation (9.8 volts, 40.4 per second) for six seconds.

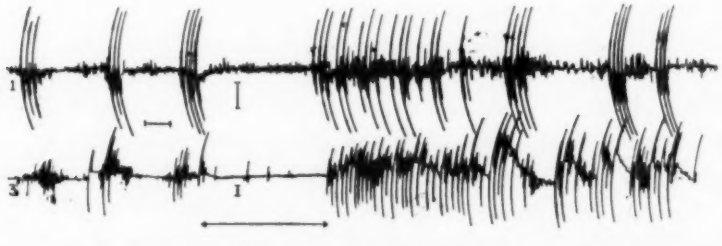


Fig. 10.—Effect of hypothalamic stimulation (6.3 volts for ten seconds) on the strychninized cortex (auditory area [*1*], motor area [*3*]). Note the suppression of convulsions during, and "rebound" after, stimulation.

strychninized cortical area. Stimulation with 3.6 volts decreases greatly the number of spikes, whereas these spikes increase in frequency under the influence of stimulation with 9.8 volts applied to the sciatic nerve. The nonstrychninized areas show relatively large potentials during the period

of stimulation with 9.8 volts (recruitment), whereas the potentials are small on stimulation with 3.6 volts.

However, the intensity of stimulation is not the only important factor, since topographic differences in the cortex must be taken into account. This interpretation is suggested by the variation in the degree of asynchrony and recruitment resulting from a given stimulus in different cortical areas, in spite of the fact that various parts of the cortex are presumably in the same state of picrotoxinization, since the convulsant drug has been given intravenously. Thus, figure 7 shows an increase in frequency and amplitude of cortical potentials in the posterior suppressor area, whereas the spike potentials disappear in the auditory area and are replaced by smaller and more frequent potentials. In the first case signs of asynchrony and recruitment are seen; in the latter only asynchrony appears to be involved. Similar variations may be observed in the reactions of two strychninized areas (local application of strychnine) under the influence of afferent stimulation. It was not infrequently seen under such conditions that an afferent stimulus increases convulsive potentials in one area but suppresses them in another.

A final observation apparently related to the phenomena of synchrony and recruitment is illustrated in figure 10, in which an increase in convulsive discharges occurs immediately after cessation of stimulation, whereas convulsive discharges had disappeared during stimulation. It is suggested that asynchronization during stimulation, which is characterized by the disappearance of spikes and "dial" bursts, is followed by the restoration of a greater degree of synchrony for some time after the period of stimulation. This effect appears in figure 10 as increased frequency of convulsive discharges and in other experiments, not involving convulsant drugs, as an intensified burst of "dial" activity. This phenomenon has a striking resemblance to the "rebound" occurring after inhibition of reflexes.

COMMENT

The preceding observations have established the observation that stimulation of the sciatic nerve, as well as of the hypothalamus, may elicit or aggravate convulsions. Since in experiments involving the sciatic nerve this effect seems to occur only when the intensity of the stimulation is adequate to elicit pain reflexes (dilatation of the pupils, increased rate of respiration), it is suggested that nociceptive impulses are largely involved in this action. The fact that milder stimuli were ineffective is probably accounted for by the anesthetic used, since tactile stimuli may elicit convulsions in cases of jacksonian epilepsy.

The observation that stimulation of the hypothalamus may evoke or aggravate convulsions suggests that emotional processes have a similar effect, since the hypothalamus is one of the major structures involved in

emotions (see Gellhorn[16] for review of literature). This experimental evidence again is in line with clinical evidence. Concerning the neurologic basis, it may be assumed that impulses arising in the posterior portion of the hypothalamus will reach all parts of the cortex either via thalamic nuclei or, possibly, directly (Murphy and Gellhorn[17]). The electrograms of the cortex and hypothalamus show, under the influence of these stimuli, an increase in frequency and amplitude which may be so great as to lead to the typical picture of status epilepticus in pictrotoxinized animals.

It is worthy of note that, although all parts of the cortex undergo these changes, there are considerable differences in the degree of reactivity of these areas. The motor area was frequently less sensitive to picrotoxin and to the effects of afferent stimulation than other parts of the cortex. The observation that in a number of experiments the suppressor areas were particularly reactive to picrotoxin and to nociceptive impulses will be investigated further.

Although the final state of picrotoxin poisoning is characterized by complete synchrony of cortical and hypothalamic discharges,[18] it was noted that at earlier stages the electrical activity in the hypothalamus and the cortex may not run a parallel course. The appearance of "convulsive" discharges in the hypothalamus may occur without a corresponding increase in the "convulsive" activity of the cortex. It is suggested that although a close relation exists between hypothalamic and cortical activity (Obrador,[19] Kennard,[20] Murphy and Gellhorn[20a]), the rate of the convulsive activity of the cortex is probably not determined by the hypothalamus in spite of the fact that the latter plays an important role as a trigger mechanism.

The effect of afferent impulses on the cortex under convulsive conditions apparently is governed by the same factors which have been found to determine their action under nonconvulsive conditions.[21] These changes

16. Gellhorn, E.: Autonomic Regulations, New York, Interscience Publishers, Inc., 1943.

17. Murphy, J. P., and Gellhorn, E.: Further Investigations on Diencephalic-Cortical Relations and Their Significance for the Problem of Emotion, J. Neurophysiol. **8**:431-448, 1945.

18. Hoefer and Pool (Conduction of Cortical Impulses and Motor Management of Convulsive Seizures, Arch. Neurol. & Psychiat. **50**:381-400 [Oct.] 1943) made similar observations in electrically induced convulsions.

19. Obrador, S.: Effect of Hypothalamic Lesions on Electrical Activity of Cerebral Cortex, J. Neurophysiol. **6**:81-84, 1942.

20. Kennard, M. A.: Effect on EEG of Chronic Lesions of Basal Ganglia, Thalamus, and Hypothalamus of Monkeys, J. Neurophysiol. **6**:405-416, 1943.

20a. Murphy and Gellhorn, footnotes 11 and 17.

21. The pertinent literature is cited in an earlier paper of ours.[15]

in synchrony and recruitment appear to be adequate to explain the effect of afferent impulses on cortical potentials. Since spikes are considered to be the expression of a hypersynchrony of the neurons from which these potentials are recorded, it is easy to see that afferent impulses abolish temporarily convulsive discharges because they induce asynchrony in the cortical cells. The increase in size and/or frequency of convulsive potentials observed after stimulation of afferent nerve fibers in picrotoxinized animals is understandable if it is assumed that many more neurons become activated. In spite of greater asynchrony of those cells which were active prior to stimulation, more neurons will then beat in unison and give rise to spike discharges.

In any given cortical area the degree of recruitment, and thereby the chance to precipitate or intensify convulsive potentials, depends on the intensity of the stimulus. However, various cortical areas may react differently. This is illustrated by the fact that some develop convulsive activity earlier and to a greater degree than others and that a given afferent stimulus may cause an increase in spikes in one area and diminution or disappearance in another. These observations suggest that picrotoxin, as well as afferent stimulation, may call into action a widely different number of neurons in different cortical areas. Excitability may be measured not only by the threshold stimulus which causes asynchrony but also by the intensity of a stimulus which induces recruitment. It appears that cortical regions which are in a state of higher excitability than others react to afferent stimulation with an intensification of convulsive discharges, whereas areas of lesser excitability show the opposite effect.

These observations suggest that afferent impulses may have a dual effect on overt convulsions, decreasing or increasing them according to the intensity of stimulation. Although the latter effect was frequently seen, we failed to get evidence of suppression of overt convulsions through afferent impulses. This may be related to the fact that overt convulsions occur in the anesthetized cat only at fairly high degrees of picrotoxinization. Under these conditions, afferent stimuli are more likely to produce asynchronization plus recruitment than a lessened degree of synchrony alone. However, it is possible that weaker stimuli than were used in the present investigation and non-nociceptive impulses may accomplish this effect.

Finally, it should be mentioned that, after suppression of convulsive activity during stimulation, a greatly increased convulsive discharge may follow cessation of the stimulus. A similar "rebound" phenomenon was frequently noted in cats anesthetized with "dial" which had not received injections of convulsant drugs. Sciatic and hypothalamic stimulation was followed in these animals by a group of "dial" bursts of greatly increased amplitude. Often they occurred at smaller intervals than under control

conditions. Occasionally it was seen that "dial" bursts, which were absent in a cortical area prior to stimulation, appeared immediately after it. The normal and the picrotoxinized cortex, again, act here according to the same rules. A period of lessened synchrony occurring during stimulation of afferent nerves is followed by one of increased synchrony. This leads in the normal cat anesthetized with "dial" to grouped "dial" bursts, whereas in picrotoxinized cats the hypersynchronization appears in the form of an increased burst of spike potentials. Whether the concept that the rebound is based on hypersynchrony is applicable to the physiology of reflexes in which this phenomenon is commonly found (Creed and collaborators[22]) cannot be stated at present.

SUMMARY

The influence of afferent impulses on convulsive movements and on cortical and hypothalamic potentials was studied. The afferent impulses were induced by mechanical or electrical stimulation of the sciatic nerve or by electrical stimulation of the posterior portion of the hypothalamus. Observations were made at various degrees of picrotoxin poisoning. The following results were obtained on cats anesthetized with "dial":

With adequate degrees of picrotoxinization, stimulation of either the sciatic nerve or the hypothalamus induced convulsions for various periods during and after stimulation. Ligation of the sciatic nerve seemed to be the most effective procedure. If slight convulsions existed prior to the stimulation, afferent stimuli might greatly aggravate these convulsions.

If convulsions were precipitated or intensified as the result of afferent stimuli, the cortical potentials increased in amplitude and frequency. In a number of observations large, frequent spike potentials, resembling those seen in cases of status epilepticus, occurred.

The study of cortical and hypothalamic potentials under the influence of hypothalamic and sciatic stimulation in picrotoxinized animals revealed that hypothalamic and cortical "convulsive" activity may be dissociated. It is concluded that, although afferent impulses originating in the hypothalamus may initiate or intensify convulsions, the hypothalamus does not seem to determine the rate of cortical "convulsive" activity in these experiments.

It appears that the motor area is not particularly sensitive to picrotoxin, since sensory and suppressor areas may show larger and more frequent spikes. Consequently, severe "convulsive" discharges may be precipitated in nonmotor areas of the cortex as a result of afferent stimuli in the absence of overt convulsive movements.

22. Creed, R. S.; Denny-Brown, D.; Eccles, J. C.; Littell, E.G.T., and Sherrington, C. S.: Reflex Activity of the Spinal Cord, New York, Oxford University Press, 1932.

The study of cortical potentials in cats subjected to intravenous injections of picrotoxin or to local strychninization shows that an increase, as well as a decrease, in "convulsive" activity may result from afferent stimuli. Other conditions being equal, the former effect is due to strong, and the latter to weak, stimuli. Intensification of "convulsive" potentials seems to be associated with increased recruitment and decreased synchronization, whereas suppression of convulsive potentials is accompanied with decreased synchronization only. On cessation of stimulation, increased "convulsive" discharges (rebound) may follow suppression of "convulsive" potentials during stimulation.

Quantitative differences in the convulsive reactivity of different cortical areas account for the fact that an afferent stimulus may increase "convulsive" potentials in one area and decrease them in another.

University of Minnesota Medical School (14).

WINKING-JAW PHENOMENON

ROBERT WARTENBERG, M.D.
SAN FRANCISCO

MARCUS GUNN PHENOMENON

AT THE MEETING of the Ophthalmological Society of the United Kingdom, on July 6, 1893, the London Ophthalmologist R. Marcus Gunn (1822-1887)[1] presented a paper entitled "Congenital Ptosis with Peculiar Associated Movements of the Affected Lid." His case was that of a 15 year old girl with congenital ptosis of the left eyelid.

> She complained . . . of the fact that, while eating and occasionally while speaking, the (left) lid is rapidly jerked upwards . . . When about five weeks old it was noticed that when she was sucking the breast her left upper eyelid "nearly went up out of sight" . . . On lateral movement of her jaw to the right side (left external pterygoid) the left upper lid is raised quickly and powerfully, and this position of the lid is maintained as long as the jaw is kept drawn to the right.

This phenomenon from the very first evoked great interest. A committee of three neurologists and one ophthalmologist, headed by W. R. Gowers, was appointed by the Ophthalmological Society to examine Gunn's case. The committee reported that "the prominent fact of the case is that the levator contracts when the external pterygoid is put in action, while the latter does not contract when the levator is put in action." The essential of this phenomenon in cases of unilateral ptosis, in which the levator palperbrae on one side cannot be raised voluntarily, is an associated movement of this levator contingent on the movement of the jaw toward the unaffected side. It is an associated movement from the external pterygoid muscle to the levator palpebrae muscle; thus, from the trigeminus to the oculomotor nerve. The primary mover responsible for the deviation of the mandible to the opposite side is the external pterygoid muscle (not the internal pterygoid muscle, as Kestenbaum[2] stated). It is a pterygoid-levator synkinesis. The committee expressed the opinion that the phenomenon was due to an aberrant innervation of the levator palpebrae superioris from the motor branch of the trigeminal nerve.

From the Division of Neurology, University of California Medical School.

1. Gunn, R. M.: Congenital Ptosis with Peculiar Associated Movements of the Affected Lid, Tr. Ophth. Soc. U. Kingdom **3**:283, 1883.

2. Kestenbaum, A.: Clinical Methods of Neuro-Ophthalmologic Examination, New York, Grune & Stratton, Inc., 1946, p. 314.

The phenomenon is usually known as the jaw-winking phenomenon. The term is used even in other than the English literature. The term used by Spaeth,[3] "jaw-winking associated reflex," is not physiologic and is highly confusing. The French speak of *mâchoire à clignements*, or *l'œillade de la mâchoire*. The term "jaw-winking" was criticized. Cooper[4] called it "inelegant"; Ford[5] said it was "absurd." First of all, the term is incorrect because the movement of the eyelid that automatically and immediately follows the jaw movement is not closure of the eye, as in winking, but, on the contrary, is an elevation of the eyelid. However, the term "jaw-winking phenomenon" is so strongly entrenched in the literature everywhere that it would be almost impossible to withdraw it from circulation. For reasons of historical piety, it might as well be retained.

A voluminous ophthalmologic and neurologic literature followed Gunn's original publication, which itself occupied only three pages in the society's *Transactions*. This literature left in its wake many unanswered and unanswerable questions. To Doré,[6] the Marcus Gunn phenomenon presented one of the most complicated problems of neuro-ophthalmology. The phenomenon has become so popular that many other phenomena of the ocular muscles which have no relationship to that of Marcus Gunn have been brought into connection with it. It was found that the Marcus Gunn phenomenon can be present without ptosis or any other anomaly of the eye; or the ptosis may be bilateral. Besides the ptosis, there may be paresis of other ocular muscles, or another congenital ophthalmic anomaly may coexist. The phenomenon may be familial or hereditary. It is usually congenital but may be acquired, and in case of the latter may appear at any age; it may even appear suddenly, for instance, after concussion of the brain. The synkinesis may remain constant for life, may be transient or may progress. It may disappear while the ptosis remains.

The primary movements which bring about the automatic elevation of the eyelid are said to be: opening of the mouth only; movement of the lips; movement of the jaw to the unaffected side only; protrusion of the jaw; clenching of the teeth; whistling; puffing the cheeks; chewing; swallowing; singing; inhaling; sticking out the tongue; movements of the

3. Spaeth, E. B.: The Marcus Gunn Phenomenon, Am. J. Ophth. **30**:143, 1947.

4. Cooper, E. L.: The Jaw-Winking Phenomenon, Arch. Ophth. **18**:198 (Aug.) 1937.

5. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944, p. 220.

6. Doré: Mouvements involontaires de la paupière supérieure associés a ceux commandés par les autres nerfs crâniens (Maladie de Marcus Gunn), Clin. opht. **21**:475, 1916.

homolateral eye, closing the heterolateral eye, and turning the head to the ptotic side. Electric stimulation of the cortex may also produce the phenomenon. It has also been found that this synkinesis occurs only on looking downward. Some cases reported would thus indicate that not only movement of the mandible (fifth nerve) but also movement of the muscles innervated by other nerves, such as the third, seventh, ninth and twelfth, can produce this synkinesis. Whether all these observations are correct, whether the elevation of the lid can occur on innervation of muscles other than those supplied by the fifth or the third cranial nerve remains to be proved. All that has been added to the symptomatology of the Marcus Gunn phenomenon increases the complexity of the problems involved. Despite this great variety of the primary movements, the essential stimulus for the synchronous elevation of the ptotic lid in this phenomenon seems to be the movement of the mandible to the side opposite the ptotic lid. In studying the literature, one gains the definite impression that under the term "Marcus Gunn phenomenon" heterogenous movements have been described, movements that need stricter classification and separation.

The question whether there is an inverted Marcus Gunn phenomenon, i.e., closure of the eye on movement of the mandible, has been answered in the affirmative by some investigators. The inverted Marcus Gunn phenomenon has been discovered and rediscovered several times, so again by Halpern[7] as late as 1944. The inverted Marcus Gunn phenomenon is known as the Marin Amat syndrome, on the basis of this author's publications in 1918, 1919 and 1930. However, this phenomenon was described earlier by Müller-Kannberg[8] in 1894 and by Higier[9] in 1902. In a separate article, I have made the attempt to prove that this "inverted Marcus Gunn phenomenon" is not an associated movement, in which, as in the original Marcus Gunn phenomenon, the primary mover originates in the trigeminal muscles, but is nothing else but the very common associated movement seen often in partial recovery from facial palsy. It is thus an intrafacial associated movement, not a trigeminofacial associated movement.

However, in the Marcus Gunn phenomenon the associated movement is not reversible: The mandible does not move when the levator palpebrae is innervated.

---

7. Halpern, L.: The Inverted Gunn Phenomenon, Acta med. orient. **4**:342, 1945; Zur Phänomenologie einer motorischen Korrelation zwischen Lid und Kiefer, Schweiz. Arch. f. Neurol. u. Psychiat. **54**:134, 1944.

8. Müller-Kannberg: Eigentümliche Mitbewegung eines ptotischen Lides bei Unterkieferbewegungen, Der ärztliche Praktiker **7**:1177, 1894.

9. Higier, H.: Zur Klinik der eigentümlichen Mitbewegungen des paretischen Lidhebers und Lidschliessers, Deutsche Ztschr. f. Nervenh. **21**:306, 1902.

WINKING-JAW PHENOMENON

In the following discussion, an automatic, involuntary movement of the mandible which takes place on reflex or voluntary closure of the eye is reported. It is thus an inverted and reversed Marcus Gunn phenomenon and could be called the winking-jaw phenomenon. This movement has been brought into relationship with the Marcus Gunn, as a widely known phenomenon, but has no direct connection with it and is, so to say, a movement on a quite different level.

This phenomenon consists in the following components: When the examiner touches one cornea, as for elicitation of the corneal reflex, a quick, brisk movement of the mandible to the contralateral side takes place. It sometimes seems that the mandible also moves forward slightly.

The cornea should be touched not lightly, but with some force. The effort should be to elicit a vigorous closing of the eye. Mere blinking is not sufficient. It is best not to use cotton or paper, as is usually done for elicitation of the corneal reflex, but to use a solid glass applicator and to exercise some pressure on touching the cornea. Pressure alone on the cornea, without producing winking, has no effect on the mandible, for instance, pressure on the eyeball when the eyelid is closed does not evoke the slightest movement of the mandible, even if considerable force is employed. The movement of the mandible takes place simultaneously with closure of the eye. The deviation of the lower jaw occurs essentially on a horizontal level. The forward movement is minimal and occurs with such rapidity that it may be easily overlooked. The lateral movement is exhaustible, but returns after a pause. It is inconstant, so to speak, whimsical, and sometimes does not appear when most expected. Apparently it depends on many factors, the nature of which is not entirely known at present. Any muscular tension will interfere with the appearance of this phenomenon. It is, therefore, essential that the patient relax the eyelids and muscles of the jaw and allow the mandible to hang loosely. This is often difficult for the patient to achieve, and he must try again and again.

There are rare cases in which the movement of the mandible to the contralateral side may be evoked on touching either cornea. It is interesting to note that in these cases the movement of the mandible on touching the cornea on one side still occurs at all. A priori, it must be assumed that the simultaneous consensual closure of the eye on touching the contralateral cornea should prevent any movement of the mandible. For instance, when this movement is bilateral, touching the left cornea would produce movement of the mandible to the right, but the consensual blinking of the right eye should have evoked a movement of the mandible to the left. These two movements should counteract each other, provided they are of the same strength. This apparently is not

the case, since when the movement of the mandible can be evoked by touching of either cornea this movement can be strong to either side. This can mean only that the closure of the eye on the side of the touched cornea must be much stronger than the consensual movement on the other side. Accordingly, the contralateral movement of the mandible to the side opposite the touched cornea is much stronger and easily suppresses the slighter movement of the mandible to the other side. I am not aware of any quantitative studies which have been made on the comparative strength of closure of the homolateral and the heterolateral eye on touching of one cornea.

When movement of the mandible can be elicited by touching either cornea, simultaneous touching of both corneas produces a slight forward movement of the lower jaw.

Exactly the same movement of the mandible to the contralateral side takes place when the patient is asked to close the eye on the side on which the phenomenon can be elicited by touching the cornea, and to close it briskly and forcefully. Thus, the movement of the mandible takes place both on reflex and on voluntary contraction of the orbicularis oculi. The movement on voluntary contraction has the same characteristics as it has on reflex contraction, but is generally much weaker, much less constant and easily exhaustible. It takes place only on a quick and strong contraction, which is often difficult to achieve.

This phenomenon has not been found in normal subjects. In a few cases, to be sure, it appeared that a very slight, a very weak and exhaustible movement might have taken place. This phenomenon is not found in children. It is not exaggerated in neurotic persons, who show an exaggeration of the deep muscle reflexes. It is never found in patients with extrapyramidal lesions. If positive, it is more often unilateral. With cortical and with capsular lesions leading to hemiplegia, the movement of the jaw can be elicited only by touching the cornea on the side of the hemiplegia, the mandible moving to the opposite side. But this is by no means always the case. The phenomenon is not elicited in cases of old, or of slowly progressive, hemiplegia. It can best be demonstrated in the first few weeks after the hemiplegic attack. In cases of fresh apoplexy, it might be the leading sign indicating a localized cortical lesion and its site. It is not seen after epileptic attacks. When seen in cases of amyotrophic lateral sclerosis, it is an early indication that the pyramidal degeneration has crept up to the brain stem and has affected the corticopontile tracts of the trigeminus nerve. Bilaterally the phenomenon is seen with amyotrophic lateral sclerosis and with diffuse pontile lesions. In the former disease the phenomenon is found in its most pronounced form. The movement of the mandible on touching the cornea may occur so violently and may be of such a long range that one is amazed that it has remained unnoticed so long.

The following case illustrates the importance of the winking-jaw phenomenon. A man aged 22 sustained a fracture of the skull in an automobile accident. Lumbar puncture revealed bloody cerebrospinal fluid. He was in coma for two weeks. During this time there seemed to be, according to the referring physician, mild weakness of the right side, from which the patient apparently recovered. He showed a fairly severe degree of aphasia after recovering consciousness. When I examined the patient for the first time, four months after the injury, he had mild headaches and showed a slight weakness of central type on the right side of the face, with diminution of palpable vibration of the upper right lid but without notable functional disturbance of the facial muscles. The muscles supplied by the trigeminal nerve presented no functional disturbances; there was no deviation of the mandible, and the corneal reflex was normal. The masseter muscle on the right side was felt to be less massive than that on the left when the patient clenched his teeth. He also showed a slight degree of amnestic aphasia, with dyslexia and dysgraphia. There were no pyramidal signs in the right extremities and no motor disturbances.

When the examiner touched the right cornea, as for elicitation of the corneal reflex, the homolateral and consensual corneal reflexes were found to be normal, but the mandible, simultaneously with the winking of the eye, moved briskly to the left. The same movement of the mandible occurred, but much less regularly, when the patient closed his right eye forcefully and quickly against the resistance of the finger of the examiner, who tried to lift the upper lid. No movement of the mandible took place when the left cornea was touched or when the patient closed his left eye.

On the second examination, six and one-half months after his injury, it was found that the aphasia, dyslexia and dysgraphia had improved greatly. The functional status of the muscles in the distribution of the facial and trigeminal nerves was the same. In the meantime, the patient had had two attacks which were classified as epileptic. The winking-jaw phenomenon was the same.[10]

Of the whole clinical picture in this case, it must be said that the winking-jaw phenomenon was the most striking feature, and the only one which drastically illustrated the supranuclear involvement of the right trigeminal nerve. It must be

---

10. A third examination took place sixteen months after the injury. General epileptic attacks of grand mal character had increased in severity and frequency despite treatment. These attacks, however, did not offer any focal clue. Petit mal attacks had started also. The only objective findings on neurologic examination were: mild aphasia, particularly of amnestic type; slight diminution of the palpable vibration of the right upper lid and a very strong winking-jaw phenomenon elicited from the right eye. Electroencephalographic examination (Dr. R. B. Aird) was reported as follows: "A generalized and suggestively paroxysmal dysrhythmia of nonspecific type, which appeared off and on throughout the record and was slightly exaggerated during hyperventilation, was compatible with a convulsive susceptibility of slight or moderate degree. In addition, there was considerable evidence to suggest changes of a presumably degenerative character in the low postcentral, the anterior temporal and possibly the precentral and posterior temporal regions on the left." Pneumonencephalographic study (Dr. Aird) revealed the following changes: "The lateral ventricles were considerably enlarged, the left more than the right. There was a marked shifting of the whole ventricular system to the left. There was no filling of the subarachnoid channels except anteriorly." Dr. H. C. Naffziger stated his opinion that surgical intervention was not indicated.

assumed that this patient had a diffuse lesion of the left cerebral hemisphere, affecting particularly the left frontomotor area.

SO-CALLED CORNEOMANDIBULAR REFLEX

Elicitation of involuntary movement of the mandible to the opposite side on touching one cornea is not a new phenomenon. It was described first by von Sölder[11] in 1902, as the "corneomandibular reflex." He stressed the fact that the movement of the mandible occurred in a horizontal level and that no opening or closing of the mouth took place. The movement was due to an isolated contraction of the external pterygoid muscle. The reflex, which was found very easily exhaustible, was regarded as a physiologic one, though not constant. In some normal persons it was found only in traces. The functional association between the cornea and the external pterygoid muscle was regarded as "peculiar," and one on which comparative physiology might throw some light. It was looked on as a purely intratrigeminal reflex. In a short critical note of 1903, Kaplan[12] expressed doubt concerning the reflex nature of this phenomenon and raised the question whether an associated movement existed here between the orbicularis oculi muscle and the external pterygoid muscle. In 1904 von Sölder[13] violently rejected the idea of the possible synkinetic nature of his phenomenon. Its reflex nature seemed to him to be so clearly and directly evident from the facts that he regarded it as superfluous to substantiate his view. In 1918 Trömner[14] demonstrated a "new bulbar reflex," twisting of the mandible to the opposite side on touching the cornea. This was regarded as an example of a purely trigeminal reflex, as is the masseter reflex. Von Sölder[15] reminded Trömner that he had discovered this reflex sixteen years previously and stressed that it is a physiologic reflex which, under pathologic conditions, occasionally appears particularly distinct. In a special article devoted to this "pterygocorneal reflex," as Trömner[16] now called it, he stressed its reflex nature. In his opinion, it was a special kind of corneal reflex. It had never been observed in normal persons but had been seen only in patients with suprabulbar lesions of the brain.

---

11. von Sölder, F.: Der Corneo-Mandibularreflex, Neurol. Centralbl. **21**: 111, 1902.

12. Kaplan, J.: Zur Frage des Corneo-mandibularreflexes, Neurol. Centralbl. **22**:910, 1903.

13. von Sölder, F.: Ueber den Corneo-mandibularreflex, Neurol. Centralbl. **23**:13, 1904.

14. Trömner, E.: Bulbärreflex (Pterygo-Cornealreflex), Neurol. Centralbl. **37**:334, 1918.

15. von Sölder, F.: Bemerkung zu Trömners Petrygo-Cornealreflex, Neurol. Centralbl. **37**:432, 1918.

16. Trömner, E.: Der Pterygo-Cornealreflex, Ztschr. f. d. ges. Neurol. u. Psychiat. **78**:306, 1922.

The phenomenon described by von Sölder and Trömner attracted little attention in the German literature and remained almost completely unnoticed outside Germany. It is not mentioned in the common English textbooks. It was the subject of investigation by several Russian authors (Goldin,[17] Zalkan and Frenkel,[18] Frenkel[19]). To the last author the corneopterygoid reflex appeared as a purely intratrigeminal reflex, like the masseter reflex. No reference was made to it in the detailed French monograph on the corneal reflex by Cerise and Thurel.[20] In reviews, it was declared as being of no diagnostic importance (von Michel,[21] Wilbrand and Sänger,[22] Bartholomé[23]). It is usually regarded as a normal phenomenon (Fuchs,[24] Kroll[25]).

As assistant to Foerster in 1923, I observed that he was very much interested in this phenomenon. He[26] was not inclined, as was Trömner, to deny its presence completely in normal persons, but stressed "that this reflex can by no means be counted with the reflexes which are constantly elicited in normal persons." He[27] found it exaggerated in cases of peripheral facial palsy. Somewhat in contradiction to these statements, Foerster[28] said:

> . . . The pterygocorneal reflex presents, in my oninion, one of the finest signs of damage of the cortical center for the mandible or of the efferent tract arising from this center.

---

17. Goldin, A. M.: Corneo-Mandibular Reflex, Sovet. psikhonevrol. **12**:99, 1936.

18. Zalkan, D. M., and Frenkel, A. B.: Diagnosis of Certain Facial Reflexes, Corneal Reflex, Corneopterygoid Reflex, Flatan Reflex and Marineska-Radovichi Reflex, Sovet. psikhonevrol. **14**:30, 1938.

19. Frenkel, A. B.: Semeiotic Significance of the Corneopterygoid Reflex, Vrach. delo **22**:759, 1940.

20. Cerise, L., and Thurel, R.: Le réflexe corneen en pathologie nerveuse, Rev. neurol. **1**:915, 1932.

21. von Michel, J.: Die Krankheiten der Augenlieder, in Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, W. Engelmann, 1908, vol. 5, p. 351.

22. Wilbrand, H., and Sänger: Die Neurologie des Auges, Ergänzungsband, Munich, J. F. Bergmann, 1927, pt. 1, p. 28.

23. Bartholomé, H.: Ueber Gesichtsreflexe, Inaug. Dissert., Freiburg, 1932, p. 26.

24. Fuchs, A.: Einführung in das Studium der Nervenkrankheiten, Leipzig, F. Deuticke, 1911, p. 78.

25. Kroll, M.: Die neuropathologischen Syndrome, Berlin, Julius Springer, 1929, p. 209.

26. Foerster, O., in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 6, p. 239.

27. Foerster,[26] vol. 3, p. 596.

28. Foerster,[26] p. 268.

The only publication in English which deals with this phenomenon is that of Ornsteen.[29] He spoke of palpebromandibular synkinesis and rightly differentiated this phenomenon from the Marcus Gunn type. In his case, "every voluntary and involuntary movement of the eyelids was synchronously associated with an involuntary short, sharp movement of the jaw upward and forward, and if the mouth was held open the jaw would snap shut with a click of the teeth." When the patient held his mouth slightly open, the mandibular movement became exaggerated. Ornsteen stated: "I have been unable to find a reference to a similar observation in the literature." However, there is no doubt that the observation reported by Ornsteen must be regarded as identical in its essential points with the corneomandibular reflex of von Sölder, which was thus again rediscovered.

IS THE VON SÖLDER PHENOMENON A REFLEX OR AN ASSOCIATED MOVEMENT?

To all investigators of this phenomenon, except to Kaplan and Ornsteen, it appeared to be a reflex. It was called the corneomandibular reflex, the pterygoid-corneal reflex or the corneopterygoid reflex. Several authors emphasized that this phenomenon is a purely intratrigeminal reflex, like the masseter reflex. Without going into a discussion of the complex problem of reflex and associated movement, one would better call it an associated movement, for the following reason: The automatic involuntary movement of the mandible to the contralateral side takes place not only on tactile stimulation of the cornea, as in elicitation of the corneal reflex, but also on active closure of the eye. Von Sölder,[11] however, stated: "On voluntary closure of the eye there never occurs a twitching of the mandible comparable to the corneomandibular reflex." This statement is not correct. It is true that on ordinary closure of the eye no mandibular movement occurs. But it certainly does occur when the patient closes the corresponding eye forcefully, quickly and against resistance. It is true that the mandible does not move so strongly or so constantly on active innervation of the eyelid as it does on touching the cornea and eliciting the corneal reflex. However, such movement has been observed so distinctly that there can be no doubt that it followed in the wake of an active innervation of the eyelid. Here the same is true as in the Marcus Gunn phenomenon, in which only forceful movement of the mandible elicits the associated rising of the upper lid. On repeated examinations, it has been seen again and again that normal, weak closure of the eye is without effect on the mandible, whereas

29. Ornsteen, A. M.: Palpebromandibular Synkinesis in a Patient with Acute Polyneuritis and Facial Diplegia, Arch. Neurol. & Psychiat. 34:625 (Sept.) 1935.

forceful, quick closure is accompanied with a movement to the contralateral side.

It is thus understandable why von Sölder in his cases of the "corneomandibular reflex" could not achieve a movement of the mandible on stimulation of the sclera or the conjunctiva or on elicitation of the optic lid reflex, but only on touching the cornea; only with the latter is there a forceful contraction of the orbicularis oculi muscle, and only on such a contraction is there an associated movement of the mandible. In all other instances the primary movement of the orbicularis oculi is too weak. In the case of Ornsteen, the mandible moved synchronously with each voluntary movement of the eyelids. "The patient was asked to blink his eyes voluntarily and rapidly and with as much force as he could; the blinking was accompanied by stronger movements of the mandible." In comatose persons with organic lesions of the brain von Sölder observed several times that his corneomandibular reflex was preserved, whereas the corneal reflex was absent. This could be explained more readily on the basis that this phenomenon is an associated movement and not a reflex. The reflex contraction of the orbicularis oculi may not be clearly visible on touching the cornea and the corneal reflex may apparently be absent, but the associated movement of the mandible may still be present. It is well known that in associated movements the primary mover may be minimal, may lead to no displacement of the muscle but may still lead to visible and forceful secondary (associated) movements. The primary mover may show no visible movement at all, may even be paralyzed completely; and yet an impulse sent to this muscle, though having no effect on the particular muscle, may evoke a strong associated movement in other muscles. This one sees again and again in associated movements of the oculomotor muscles. It is also well documented in Bell's phenomenon, as seen in complete facial paralysis. An attempt to close the eye may be fruitless, may not affect the eyelids but may still evoke a sharp upward movement of the eyeball.

The phenomenon impresses one immediately as being an associated movement, an associated movement between the muscles innervated by the facial nerve, on the one side, and the muscles innervated by the trigeminal nerve, on the other. It is thus a faciotrigeminal synkinesis, or, with reference to the organs moved, a palpebromandibular synkinesis. According to the essential muscles involved, it is an orbiculopterygoid synkinesis. It takes place in the area of the cranial nerve which is innately, so to speak, a playground for associated movements. This is esespecially true of the muscles of the eye. Several reviews (Carmichael and Critchley,[30] Coppez[31]) show the enormous variety of associated

30. Carmichael, E. A., and Critchley, M.: The Relations Between Eye Movements and Other Cranial Muscles, Brit. J. Ophth. **9**:49, 1925.

movements which involve the ocular and neighboring muscles. Some of them are physiologic, some definitely pathologic and some borderline.

FOUR TYPES OF ASSOCIATED MOVEMENTS OF THE OCULAR MUSCLES

The bewildering variety and complexity of these associated movements make an attempt at their classification imperative, but this should be on something more than purely descriptive grounds. Approaching the problem from a developmental standpoint, one may assume that these associated movements originate at different physiologic and embryonic levels.

1. The associated movements of the facial muscles represent the first type, originating, so to speak, at the lowest level. After partial recovery of these muscles following supranuclear, nuclear or peripheral lesions, the muscles lose their ability to perform fine, single movements but, instead, perform mass movements in which all the muscles act as a unit, "all for one." As is well known, all the single facial muscles, now capable of an isolated contraction, stem from a common ancestor, a muscle which was working *in toto*. Even a remote muscle of the facial nerve springs readily into action on the slightest voluntary or reflex movement of another muscle of this nerve. This simple thesis explains the great number of phenomena observed in associated movements of the facial muscles. These phenomena are known as signs or reflexes, often with proper names attached. There is a common denominator for all of them: associated mass movements, instead of single movements. A dedifferentiation of movements has taken place. A phylogenetic regression, a throwback, has brought a revival of the old primitive function of the facial muscles, which were at one time a single, compact and inseparable muscle.

2. The second level of the associated movements of the ocular muscles is represented by those occurring after partial recovery from oculomotor palsy. Here, the associated movements do not involve all the muscles innervated by the diseased nerve, as they do after facial palsy; only two affected muscles predominate—the levator palpebrae and the rectus internus. Thus, when the patient tries to innervate any part of the oculomotor nerve, for instance, when he looks downward, these two muscles spring into action: The patient automatically lifts his lid and adducts his eye. The lifting of the lid may be pronounced. The action of the levator palpebrae is particularly linked with that of the rectus internus; the eyelid lifts automatically on adduction of the eye. These two movements, i.e., adduction of the eye and elevation of the eyelid have

31. Coppez, H.: Essai de classification de quelques syncinésies ocularies, Rev. oto-neuro-opht. **10**:12, 1932; J. belge de neurol. et de psychiat. **32**:245, 1932.

survived best and become predominant. Out of the ruins of the oculomotor innervation there is a resurrection of these two movements, which in some way have become even stronger than before. Both are fundamentally essential for the fixation of an object in the act of vision: lifting of the upper lid and adduction of the eye. These two movements might be compared with the flexor movements of the legs in cases of pyramidal lesions. They represent the "fixation reflex," which may be regarded as analogous to the "flexor withdrawal reflex" of the legs.

Thus, like the facial muscles, the muscles innervated by the oculomotor nerve have associated movements of their own which in no way are connected with the muscles innervated by the trigeminal or facial nerve as primary movers. These associated movements occur exactly as in the facial muscles after incomplete recovery from a palsy. The only difference is that after palsy of the oculomotor nerve the two muscles which are apparently phylogenetically the strongest—the levator palpebrae and the rectus internus—move automatically whenever an impulse is sent to any muscle of the oculomotor nerve, though this muscle may be more or less completely paralyzed.

3. The third level of associated movements is represented by movements performed by muscles which have undergone a much deeper segregation and separation than have the facial muscles, and at a much earlier stage of their phylogenetic development. When, through some morbid process, a dedifferentiation of these muscles takes place, the associated movements between these two muscles which formerly belonged together do not occur so readily, and only after some profound morbid change. The winking-jaw phenomenon, the orbiculopterygoid associated movement described here, could be explained in this way. The orbicularis oculi muscle and external pterygoid muscle formerly belonged together, as did the different parts of the facial muscles. A supranuclear lesion—a congenital malformation or an acquired pathologic process—allows these two muscles to work together again, as is the case with the different components of the facial muscles. When one looks at an illustration of the orbicularis oculi and external pterygoid (Cunningham[32]) and considers the proximity of these muscles and their somewhat parallel course, the idea of their close relationship seems not illogical. The proof that these two muscles phylogenetically or ontogenetically belonged together is still lacking.

4. The fourth, and highest, level of associated movements is that of topographically remote, but physiologically related, muscles. This is seen in the Marcus Gunn phenomenon. Here the associated movement is much more complicated, involves other than neighboring muscles, has

32. Cunningham, D. J.: Cunningham's Text-Book of Anatomy, ed. 3, New York, Oxford University Press, 1931, fig. 340, p. 398.

a higher physiologic importance and serves a more vital function than the three types which have already been mentioned. Here an old, complicated, functional mechanism is released by some malformation or disease. While associated movements after injury to the third or seventh nerve are, so to speak, a local affair, an intrinsic function of neighboring muscles, without great physiologic significance, this is not so in the case of the Marcus Gunn phenomenon. Here the associated movement involves different territories, unearths old, more important, physiologic functions. It is not a local, but an "interstate," affair.

All four types of associated movements can be regarded as expressions of phylogenetic regression. In intrafacial associated movements it is evident; it is apparent in intraocular associated movements; it is very probable in the winking-jaw phenomenon; it is very reasonable to assume that the same mechanism of release is at work in the jaw-winking phenomenon of Marcus Gunn.

MARCUS GUNN PHENOMENON VIEWED PHYLOGENETICALLY AND ONTOGENETICALLY

Much has been written about the pathogenesis of this peculiar syndrome. But all the different theories can be placed in two main categories. According to one line of thought, abnormal connections exist, either between the nuclei or between the trunks of the trigeminal and oculomotor nerves. Harris[33] stated:

> . . . Occasionally there is a communication between the motor nucleus [of the fifth nerve] and the third nucleus, especially between that portion supplying the depressors of the lower jaw and the nerve to the levator palpebrae.

The famous ophthalmologist Uhthoff[34] assumed "first of all, an abnormal congenital connection between the oculomotor nerve and the nucleus of the third branch of the homolateral trigeminal nerve via the fasciculus longitudinalis posterior." Some authors spoke of "congenital misdirection of fibers." Marin Amat[35] assumed misdirection in the growth of the nerves at the periphery.

All this, of course, could not be applied to acquired cases of the Marcus Gunn phenomenon. Many careful observations by noted neurologists and ophthalmologists leave no doubt that, though the Marcus

---

33. Harris, W.: Neuritis and Neuralgia, London, Humphrey Milford, 1926, p. 242.

34. Uhthoff, W.: Ueber einen Fall von abnormer einseitiger Lidhebung bei Bewegungen des Unterkiefers, Berl. klin. Wchnschr. **25**:721, 1888.

35. Marin Amat, M.: Sur le syndrome ou phénomène de Marcus Gunn, Ann. d'ocul. **156**:513, 1919.

Gunn phenomenon is usually congenital, it may be acquired. One can only agree with Harlan,[36] who stated:

> . . . Of course, no morbid process could transfer a nerve fibril to another nucleus, and no explanation that supposes an abnormal nerve supply will serve our purpose.

Against the view that the Marcus Gunn phenomenon is due to changes in the lower nerve mechanism, the following objection, generally speaking, may be raised. The lower motor mechanism innervates only individual muscles and does not achieve such fine coordinated action between single muscles as is seen in the Marcus Gunn phenomenon. The lesion here, therefore, must be supranuclear.

The pathogenesis of the Marcus Gunn phenomenon can be more easily and more correctly understood on the basis of general knowledge of associated movements, when one assumes that nothing new or abnormal has been added here, but something has been taken away, and this something has released old, preformed mechanisms. Going down the phylogenetic ladder, one finds the movement of opening the eye associated with the opening of the mouth in wild animals when they devour their food. It has been noticed in cats during mastication and graphically illustrated by motion pictures (Pimentel[37]). Harman[38] stated:

> . . . Now if you will watch the respiration of a fish you will observe that there is an association between the movements of the jaw and the gills; when the mouth is opened the spiracle dilates. It can be well seen in the gold-fish of aquaria; when the mouth is opened for breathing or when the fish swallows its food, the operculum covering the gills swings open.

Going down the ontogenetic ladder, one commonly finds in children an associated movement of opening the eyes on opening the mouth. Children with photophobia involuntarily open their mouths in trying to open their eyes. Beaumont[39] reported the case of a child with congenital ptosis. When the child tried to raise her eyelids, she opened her mouth and closed it as soon as she stopped trying to open her eyes. An associated movement on forceful opening of the mouth, consisting of simultaneous wide opening of the eyes and spreading of the fingers, is found in children (Dräseke,[40] Steinmann[41]). Gött[42] described a com-

36. Harlan, G. C.: Case of Associated Movement of Eyelid and Jaw, Ophthalmoscope **2**:177, 1904.

37. Pimentel, P. C.: Gunn's Phenomenon, Ophthalmos **2**:238, 1941.

38. Harman, N. B.: Associated Jaw-Winking Movements, Tr. Ophth. Soc. U. Kingdom **23**:356, 1903.

39. Beaumont, W. M.: Synergic Movements of the Eyelids and Mouth, Brit. M. J. **2**:629, 1907.

40. Dräseke, J.: Ueber Mitbewegungen bei Gesunden, Deutsche Ztschr. f. Nervenh. **68-69**:344, 1921.

(Footnotes continued on next page)

plicated associated movement which he observed in normal children 1½ to 12 years of age. When they were asked to open their mouths wide, they simultaneously opened their eyes wide, stretched their arms downward and spread their fingers wide apart.

Normal adults may retain remnants of associated movements between the eye and the mouth. It was observed (Schweigger[43]) that adults, too, show a tendency to open their mouths when asked to open their eyes. Adults simultaneously open both eyes and mouth when moved by emotional stress, as in horror, astonishment or fear (Thorek[44]). Pick[45] said:

> . . . When one clenches the teeth forcibly and at the same time tries to open the eyelids wide without moving the eyes upward and without wrinkling the forehead, one can perform this only with great difficulty. But this can be performed at once, and with greater ease, when the mouth is even slightly opened.

Beaumont[39] stated:

> . . . The tendency of the mouth and eyes to open together may be readily tested by putting a finger between ones' own teeth and gripping it firmly. If the eyes are now widely opened a relaxation of the grip will be experienced. Or if the mouth be slightly opened and then the eyelids are opened to their widest extent, we shall see if we look in a mirror that there is an inclination for the mouth to open still wider. This association of eyelids and mouth is recognized in the post-operative treatment of cataract, when it is usual for some days not to allow patients food which requires biting.

All this indicates that to produce the Marcus Gunn phenomenon a new mechanism does not come into play, but, owing to some kind of release, an old dormant, latent mechanism comes to the fore. Associated movements predominate at the beginning of phylogenetic and ontogenetic development. The child is a creature that performs mass movements. Fine, isolated, single movements are a later accomplishment. This later development is characterized by segregation and disassociation of movements. Many cerebral lesions, especially of the pyramidal tracts—congenital anomalies, even peripheral lesions, the latter by *réaction à distance,* manifest themselves by a defect in differentiation. Atavistic movements, relics of formerly purposeful movements, which represent a phylogenetic and ontogenetic regression, appear. The suppressed "anlage" toward associated movements breaks through wherever opportunity presents itself.

---

41. Steinmann, I.: Ueber Mitbewegungen bei Hilfsschulkindern, Ztschr. f. Kinderforsch. **39**:83, 1931.

42. Gött, T.: Eine wenig bekannte Mitbewegung und ihr Sinn, Ztschr. f. d. ges. Neurol. u. Psychiat. **66**:93, 1921.

43. Schweigger, in discussion on Siemerling: Ueber anatomischen Befund bei congenitaler Ptosis, Berl. klin. Wchnschr. **29**:205, 1892.

44. Thorek, M.: The Face in Health and Disease, Philadelphia, F. A. Davis Company, 1946, pp. 102-109.

45. Pick, L.: Mitbewegung eines ptotischen Augenlides bei Kaubewegungen, Deutsche med. Wchnschr. **31**:484, 1905.

Since the associated movements following a pyramidal lesion doubtless represent a developmental regression, it is instructive and illuminating to compare these movements in spastic paralysis with those seen, for instance, in the Marcus Gunn phenomenon. We find, then, in both conditions paralysis of movements, but not of individual muscles which carry out these movements. This means that a muscle which is unable to perform the movement normally assigned to it may still perform such movement as part of a mass movement. In spastic paralysis affecting the left arm, for instance, the patient cannot perform the single movement of extension of the wrist. However, when this patient clenches his fist, he simultaneously performs extension of the wrist. Similar conditions are seen in the Marcus Gunn phenomenon. When requested, the patient is unable to lift the ptotic right eyelid, but this movement is easily performed as an associated movement when the patient moves his jaw to the left. This physiologic similarity speaks, of course, for the Marcus Gunn phenomenon being also a phylogenetic regression, as is an associated movement seen after spastic paralysis.

ASSOCIATED MOVEMENTS IN NORMAL PERSONS

Von Sölder[11] emphatically stated that he found his "corneomandibular reflex" in normal persons. Goldin[17] saw it four times in 100 healthy persons. Trömner[16] emphatically stated that he never found his "pterygocorneal reflex" in normal persons. Foerster[26] took the middle position. I myself have never seen the winking-jaw phenomenon in pronounced form in normal persons, but must admit that it may exist here in traces. The phylogenetic point of view propounded here provides the best explanation. Single movements are a late achievement in the development of the brain. The degree to which this development suppresses the primitive, the phylogenetically old, "anlage" toward "outmoded" associated movements becomes stronger as the person matures. The end result, of course, differs from one person to another. Some retain in traces vestigial remnants of the tendency toward associated movements. This is often seen in facial muscles. These remnants of associated movements in normal adults are sometimes combined with some other motor defect. The whole gives a clinical picture of what Dupré called *débilité motrice,* or what Meige called *infantilisime moteur.* These otherwise healthy persons who cannot be called abnormal still show some constitutional motor inadequacy. All this makes it understandable why the winking-jaw phenomenon, being a vestigial remnant of a phylogenetically old, a now extinguished, movement, may appear in traces in normal subjects. This applies particularly also to intrafacial associated movements. The statement of von Sölder that a positive corneomandibular reflex is found in normal persons cannot therefore be completely ignored.

COEXISTENCE OF VARIOUS TYPES OF ASSOCIATED MOVEMENTS

In the same person and at the same time, one type of associated movements, as previously discussed, may coexist with another type. This is clinically and physiologically of importance and of interest. The common ground of all four types makes this understandable. A certain morbid process, depending on its extension, may release one or more types simultaneously. The different movements thus generated my run parallel, may exist somewhat independently or may be antagonistic; they are coordinated, but one is not subordinated to the other. From such a combination stem clinical pictures which have been called "abnormal," "extraordinary," "amazing," "complicated" cases of this and that syndrome.

Commonest is the combination of associated movements of types 2 and 4. In cases of this type there exist simultaneously (1) intraoculomotor associated movements due to an intrinsic lesion of the third nerve itself, and (2) associated movements, as seen in the Marcus Gunn phenomenon, due to a simultaneous lesion which reestablishes the old connections between the third and the fifth nerve. In such cases, since the patient shows the Marcus Gunn phenomenon, he lifts the ptotic eyelid on movement of the mandible. But, in addition, he will lift the ptotic eyelid on looking downward or on looking inward. This is due to the existence of intraoculomotor associated movements. The elevation of the ptotic eyelid on looking downward is nothing else than the common Fuchs, or pseudo-Graefe, phenomenon seen after partial recovery from oculomotor palsy. The patient will also automatically lift the ptotic eyelid when his healthy eye is closed. This is nothing else than the well known phenomenon called by de Mello Vianna[46] *ptosis à bascule* and by Paccetti[47] *ptosi a bilancia.* There is nothing extraordinary in this phenomenon. It is simply a manifestation of one of the associated movements seen after oculomotor palsy (Wartenberg[48]). A patient with such a one-sided palsy usually fixates an object with the healthy eye; but when this healthy eye is covered, the patient is forced to fixate the object with the affected eye. To do this, he must adduct the eyeball for near vision. In doing so, he automatically and involuntarily lifts the ptosed lid. To explain this phenomenon, there is no need to assume a functional synkinesis between the levator muscle on the diseased side and the orbicularis oculi muscle on the contralateral side. It is cer-

46. de Mello Vianna, J.: Recherches cliniques sur les paralysies des muscles de l'oeil, Thesis, Paris, no. 417, 1893.

47. Paccetti, G.: Sulle paralisi funzionali dei muscoli oculari, Policlinico (sez. med.) **3**:101, 1896.

48. Wartenberg, R.: Associated Movements in the Oculomotor and Facial Muscles, Arch. Neurol. & Psychiat. **55**:439 (May) 1946.

tainly not the Marcus Gunn phenomenon, which is an associated movement between the fifth and the third nerve, but it is an assoicated movement inside the confines of the oculomotor nerve on one side. It is an associated movement of the levator palpebrae on the diseased side, contingent on the—conscious or unconscious—movement of the internal rectus on the same side.

Another possible combination of associated movements is that of type 1 and type 4. Here, a patient with congenital ptosis and the Marcus Gunn phenomenon on one side acquires a facial paralysis on the other side. If this paralysis leads to postparalytic associated movements, the following movements will occur. When the patient opens his mouth, he will lift the upper lid on the side of the ptosis, as in the Marcus Gunn phenomenon. But on the other side, that of the facial palsy, on opening of the mouth, he automatically will close the eye, owing to associated movements of the orbicularis oculi muscle and the muscles of the lower part of the face which participate in the opening of the mouth. Here lies the explanation of the peculiar cases seen by Müller-Kannberg[8] and Higier.[9]

A case of congenital Marcus Gunn phenomenon in which a facial paralysis was acquired on the same side has apparently not been clearly and unmistakably described in the literature. The case of Uhthoff[34] might belong to this category, though the antagonistic influences of the two kinds of associated movements on the orbicularis oculi are not clearly seen here.

Though the different types of associated movements discussed may occasionally coexist, and the patient may thus present a confusing picture, it is of clinical and physiologic importance to keep these types of associated movements apart, not to mistake one for another and to keep the nomenclature clean and precise. Many sins have been committed on this score. Intraoculomotor movements have been mistaken for the Marcus Gunn phenomenon, as have also the associated movements after partial recovery from facial paralysis. It is easy to distinguish these different types of associated movements, and it must be stressed that the Marcus Gunn phenomenon does not occur after facial paralysis. The contradictory statement of Jean-Sédan[49] to this effect is not correct. Of the numerous diagnostic mistakes of this kind seen in the literature, the case of Fay and Scott[50] may be mentioned. These authors demonstrated

---

49. Jean-Sédan: Trouble de l'appareil moteur des paupières, in Bailliart, P.; Coutela, C.; Redslob, E., and Velter, E.: Traité d' ophtalmologie, Paris, Masson & Cie, 1939, vol. 3, p. 1073.

50. Fay, T., and Scott, M.: Jaw Winking, Arch. Neurol. & Psychiat. **37**:208 (Jan.) 1937.

a case of "typical peripheral paralysis of the right facial nerve" and stated:

> . . . When instructed to draw up the corner of the mouth, the patient showed a slight twitching movement beneath the right eye, and it was obvious that the condition was that known as "jaw-winking."

This is certainly not what is known as the jaw-winking, or the Marcus Gunn, phenomenon, but a common associated movement occurring after incomplete recovery after paralysis of the facial nerve. It was also incorrect and confusing when Leinfelder,[51] speaking of "cases of Marcus Gunn phenomenon or jaw-winking," mentioned the work of Frenkel previously discussed.[19] This author dealt with the corneopterygoid reflex, but not with the Marcus Gunn phenomenon.

CONCLUSION

Considered as an associated movement which has been suppressed in the course of phylogenetic development and has been released by a congenital anomaly or an acquired lesion of the brain, the Marcus Gunn phenomenon fits perfectly into the general knowledge of pathologic associated movements. There is nothing mysterious about it. The Marcus Gunn phenomenon does not deserve the designation "paradox," which Massalongo[52] assigned to it. Lifting of the eyelid on opening of the mouth is just as much—or as little—paradoxic as the associated movement of the tibialis anterior muscle on flexing of the thigh, as seen in pyramidal lesions. Both are release phenomena.

In a previous publication,[48] an attempt was made to regard associated movements after injury to the seventh and third nerves as phylogenetic regression. To this view I still adhere, despite a recent (1947) statement of Spaeth[3]:

> . . . There is but little doubt that the pseudo-Graefe syndrome is a frank peripheral misdirection of regenerating third-nerve fibers. . . . The symptom complex is essentially an intermingling or misdirection of developing fifth cranial nerve fibers, and perhaps tracts, and the oculomotor nerve fibers.

There is but little doubt in my mind that all these phenomena of associated movements should be viewed from one point: that of developmental anatomy and physiology.

The phylogenetic point of view, as taken here, cannot, of course, explain every sign ever described in every case of the Marcus Gunn phenomenon or of other associated movements. But it offers a promising approach to a fruitful discussion of the complex problems involved, both in the jaw-winking and in the winking-jaw phenomenon presented here.

---

51. Leinfelder, P. T.: Neuro-Ophthalmology, in Wiener, M.: Ophthalmology in the War Years, Chicago, The Year Book Publishers, Inc., 1946, vol. 1, p. 600.

52. Massalongo, R.: Sullo jaw-winking phenomen, Riv. di pat. nerv. 17: 612, 1912.

SUMMARY

When the cornea is touched on one side, as for elicitation of the corneal reflex, an automatic, involuntary movement of the jaw to the contralateral side may occur. This has been called the winking-jaw phenomenon. It is regarded as an inverted and reversed Marcus Gunn phenomenon (jaw-winking phenomenon). Since this jaw movement occurs with supranuclear lesions of the trigeminal nerve, it is a valuable diagnostic test. Physiologically, it is regarded as an associated movement between the orbicularis oculi and the external pterygoid muscle. It is viewed as a release phenomenon due to a supranuclear lesion—malformation or disease—which has reunited these two muscles. They formerly belonged together and have been separated in the course of phylogenetic development. An attempt has been made to classify the various pathologic associated movements of the ocular muscles and to view them all, including the Marcus Gunn phenomenon, as release phenomena.

NOTE.—The article by Guiot[53] reached me too late for consideration.

University of California Medical School.

53. Guiot, G.: Valeur localisatrice et prognostique du refléxe cornéo-ptérygoïden: Le phénomène de la diduction lente du maxillaire, J. belge de neurol. et de psychiat. **44-46**:233, 1946.

RESPONSES TO THERMAL STIMULI MEDIATED THROUGH THE ISOLATED SPINAL CORD

MARTIN B. MACHT, M.D., Ph.D.*
AND
ROBERT A. KUHN, M.D.
BALTIMORE

IT IS NOW generally accepted that in mammals the essential heat-regulating mechanism of the central nervous system has a supraspinal localization; and numerous studies have proved conclusively that the functional integrity of the hypothalamus is necessary for normal temperature control. Shivering and panting, effective in raising or lowering the body temperature, do not occur if the connections between the hypothalamus and the remaining portions of the brain stem have been interrupted. Only isolated and ineffective fragments of these reactions can be elicited in animals with more caudally placed transections of the brain stem. Thus, Dworkin[1] observed shivering in bulbospinal rabbits exposed to cold, and Macht and Bard[2] evoked shivering and panting in mesencephalic and bulbospinal cats at extremely low and extremely high body temperatures. However, none of these animals was successful in combating the effects of changes in environmental temperature, and such responses, although they are interesting theoretically, are ineffective and animals so prepared remain essentially poikilothermic. Since the role of the hypothalamus in the regulation of body temperature has been fully reviewed elsewhere,[3] further elaboration is not required here.

When the spinal cord of a warm-blooded animal is transected, that portion of the body innervated by the isolated cord neither shivers nor perspires in response to changes in environmental temperature; the high-

*Formerly Captain, Medical Corps, Army of the United States.

From the Quartermaster Corps Climatic Research Laboratory, Lawrence, Mass., and the Department of Physiology, Johns Hopkins University School of Medicine, Baltimore.

1. Dworkin, S.: Observations on the Central Control of Shivering and of Heat Regulation in the Rabbit, Am. J. Physiol. **93**:227, 1930.

2. Macht, M. B., and Bard, P.: Studies on the Decerebrate Cat in the Chronic State (Motion Picture), Federation Proc. **1**:56, 1942; A Study of Long-Surviving Mesencephalic and Bulbospinal Animals, Bull. Johns Hopkins Hosp., to be published.

3. Ranson, S. W.: Regulation of Body Temperature, A. Research Nerv. & Ment. Dis., Proc. (1939) **20**:342, 1940.

er the level of transection, the more closely the animal approaches a poikilothermic state. Sherrington and Laslett[4] reported this absence of thermoregulatory responses in long-surviving spinal cats, dogs and monkeys. Their findings were substantiated by Freund and Strasmann[5] and others,[3] and the subject was reviewed by Sherrington[6] in 1924. Clark[7] confirmed these earlier reports but observed that cats with low cervical transections acquire a slow adjustment after prolonged exposure to cold, resulting in partial maintenance of body temperature when the animal is exposed to a low environmental temperature for a long period. Since this acclimatization is not accompanied with any capacity for shivering in muscles innervated from below the transection or for vasoconstruction or erection of hair in any portion of the body, it is probable that this limited regulation of temperature is humoral and may be attributed to increased activity of the thyroid, which, in turn, may be dependent on the hypophysis.[8]

An analogous state obtains in men with total transections of the spinal cord. Head and Riddoch,[9] in the first systematic survey of the capacities of spinal men, did not observe shivering below the level of transection in their subjects on exposure to cold, nor have any subsequent investigators. Similarly, thermoregulatory sweating does not occur below the level of section, although profuse "spinal sweating" is commonly seen as a component of the mass reflex.[10] This spinal sweating bears no relation to thermal stimuli except when such stimuli are effective in firing a mass reflex.[10a]

Autonomous spinal responses to locally applied thermal stimuli have received little attention since Sherrington's classic experiments on spinal animals.[11] From his studies, he concluded that no discriminatory responses

4. Sherrington, C. S., and Laslett, E. E.: Observations on Some Spinal Reflexes and the Interconnection of Spinal Segments, J. Physiol. **29**:58, 1903.

5. Freund, H., and Strasmann, R.: Zur Kenntnis des nervösen Mechanismus der Wärmeregulation, Arch. f. exper. Path. u. Pharmakol. **69**:12, 1912-1913.

6. Sherrington, C. S.: Notes on Temperature After Spinal Transection, with Some Observations on Shivering, J. Physiol. **58**:405, 1923-1924.

7. Clark, G.: Temperature Regulation in Chronic Cervical Cats, Am. J. Physiol. **130**:712, 1940.

8. Uotila, U. U.: On the Role of the Pituitary Stalk in the Regulation of the Anterior Pituitary, with Special Reference to the Thyrotropic Hormone, Endocrinology **25**:605, 1939.

9. Head, H., and Riddoch, G.: The Automatic Bladder, Excessive Sweating and Some Other Reflex Conditions in Gross Injuries of the Spinal Cord, Brain **40**:188, 1917.

10. (*a*) List, C. F., and Pimenta, A. deM.: Sweat Secretion in Man: Spinal Reflex Sweating, Arch. Neurol. & Psychiat. **51**:501 (June) 1944. (*b*) Head and Riddoch.[9].

11. Sherrington, C. S.: Qualitative Difference of Spinal Reflex Corresponding with Qualitative Difference of Cutaneous Stimulus, J. Physiol. **30**:39, 1903.

to cold or warmth were evocable in such preparations below the level of section. With reference to the flexion reflex, he stated, "Neither mere touch nor cold nor warmth (unless amounting to injurious heat) evokes the reaction."[11] These conclusions have been generally accepted, and a search of the literature reveals no positive statements regarding spinal reflexes in response to thermal stimuli. Neither Head and Riddoch[9] nor subsequent investigators mentioned such reflexes in spinal man. The present paper presents evidence that the isolated spinal cord in the cat and in man is capable of mediating certain reflex responses to thermal stimuli.

These reactions were first noted in chronic mesencephalic and bulbospinal cats prepared in the department of physiology of the Johns Hopkins University School of Medicine, where additional studies were conducted on chronic spinal animals. Preliminary observations were made on men with physiologically complete transections of the cord at the Walter Reed Hospital, Washington, D. C., in the service of Lieut. Col. Lloyd Lewis, Medical Corps, and on newborn infants and older children at the Johns Hopkins Hospital, in the service of Dr. Nicholson J. Eastman. The studies on spinal men were completed at the Cushing Veterans Administration Hospital, Framingham, Mass., in the service of Dr. William Duane, Jr.

STUDIES ON ANIMALS

When a paw of a normal cat is immersed in water, it is withdrawn and shaken vigorously. In the intact animal this response is independent of both the temperature of the water or the body temperature of the animal, and it is evident that a tactile stimulus is capable of evoking the reflex. During an investigation of the behavior of mesencephalic and bulbospinal cats in the chronic state, it was observed that these animals would withdraw and shake a paw if that paw was immersed in water the temperature of which was at a certain level above or below the body temperature of the animal.[2] Because comparatively few reflex patterns are evocable in these preparations, and because the localization of responses to thermal stimuli is poorly understood, it was decided to extend the investigation of this phenomenon.

Ten normal cats and 31 cats with lesions of the central nervous system were studied. The animals were prepared for operation as follows:

	No. of Cats
Ablation of all cortex except one frontal pole	1
Unilateral ablation of frontal pole of cortex	1
Bilateral ablation of frontal poles of cortex	2
Unilateral decortication	1
Total decortication	2
Mesencephalic and bulbospinal transection	14
Spinal transection	10

These animals were studied in the chronic state, i.e., ten days to six months after operation. Localized lesions were made in an effort to delineate the portion of the central nervous system necessary for the elaboration of the withdrawal response to tactile stimuli.

It was found that the removal of one frontal pole of the cerebral cortex resulted in loss of the tactile reflex contralaterally. Removal of all cortex except for the frontal pole of one hemisphere did not affect the tactile withdrawal reflex of the paws contralateral to the remaining cortical remnant.[2] These findings are in accord with the work of Bard and his co-workers,[12] who concluded that the control of tactile "placing" reactions of the cat is localized in the frontal poles of the cortex.

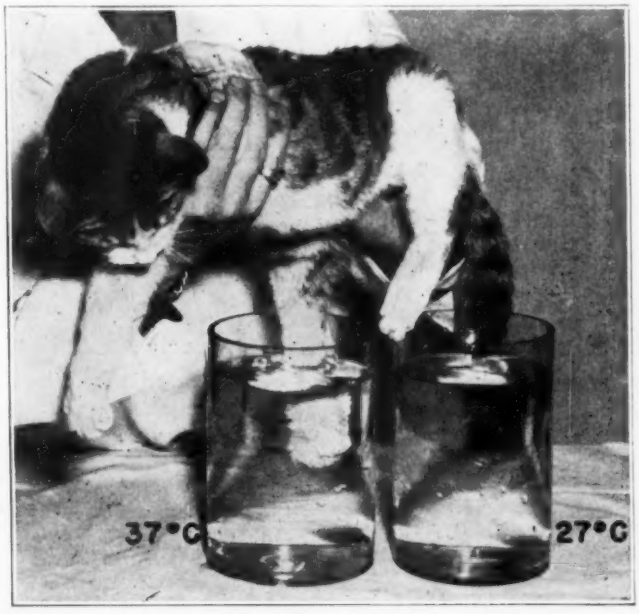


Fig. 1.—Response of spinal cat, with transection at the seventh thoracic segment, on the ninth postoperative day.

After removal of the frontal poles, no reaction was evoked unless the temperature of the medium in which the paw was immersed was at a certain level above or below the body temperature of the animal. If such an animal was tested with "cold" and "hot" water, i.e., water of a temperature below or above that of the animal's body temperature, two distinct reaction patterns could be differentiated. In each instance the response was the same—a sharp, withdrawal followed by vigorous shaking

12. Bard, P.: Studies on the Cerebral Cortex: I. Localized Control of Placing and Hopping Reactions in the Cat and Their Normal Management by Small Cortical Remnants, Arch. Neurol. & Psychiat. **30**:40 (July) 1933. Bard, P.; Brooks, C. M., and Lowry, T.: Cerebral Localization of "Hopping and "Placing" Reactions in Cats, Rabbits, and Alligators, Am. J. Physiol. **101**:3, 1932.

of the paw (fig. 1). However, the stimulus-response relationship for immersion in "cold" water was quite different from that for immersion in "hot" water.

For "cold" water, the threshold for the response was dependent on a definite relation between the temperature of the water and the body temperature of the animal. For "hot" water, the threshold for the response was relatively constant regardless of the body temperature of the animal.

These relations can best be demonstrated, and were originally noted, in chronic decerebrate cats. Because of the interruption of all connections

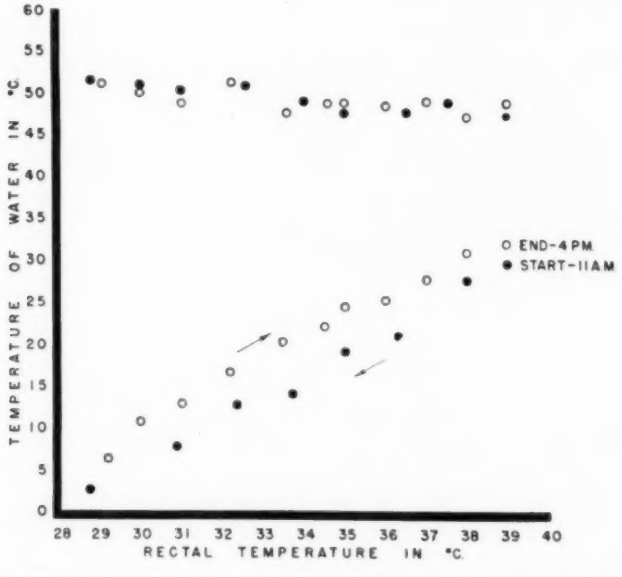


Fig. 2.—Thresholds for withdrawal of the paw of mesencephalic cat 11, on the eighty-third postoperative day. The black dots indicate values in the cold chamber, with falling body temperature; the clear circles, values in the heating chamber, with rising body temperatures.

between the hypothalamus and the remaining neuraxis, such preparations are essentially poikilothermic; it is a simple matter to raise or lower the body temperature by varying the temperature of the environment.

Figure 2 illustrates the results of an experiment performed on a mesencephalic cat on the eighty-third postoperative day. In this experiment, the threshold for withdrawal from water above body temperature was arbitrarily designated as the lowest temperature of water from which the paw was withdrawn within ten seconds. Threshold for withdrawal from water below body temperature was designated as the highest temperature of water from which the paw was withdrawn within ten seconds, The paw was carefully dried after each immersion, and an interval of at least five minutes occurred between each test. Thresholds for withdrawal

of the paw from both "cold" and "hot" water were first tested with the animal's rectal temperature at 39.0 C. The cat was then placed in the cold room, and thresholds were repeatedly tested as the rectal temperature dropped to 28.8 C. The animal was then removed from the cold room and placed in a heating chamber. Thresholds were again tested until the rectal temperature had returned to 39.0 C.

The results indicate that in the case of immersion in "cold" water the minimum difference between the rectal temperature of the animal and the temperature of the water necessary to produce a response is an approximately linear function of the rectal temperature of the animal within the range of temperatures investigated. In contrast to this, the threshold for the response produced by immersion in "hot" water is independent of body temperature; the threshold is high (approximately 50C.) and relatively constant.

On the basis of these observations, it may be assumed that in the case of immersion in "cold" water the receptors primarily involved are the end bulbs of Krause, which in the intact human subject are concerned with the sensation of cold, whereas in the case of immersion in "hot" water the receptors primarily involved are free nerve endings, which in the intact human subject are concerned with the sensation of pain.

The withdrawal reflexes to nontactile stimuli were observed in long-surviving decorticate, mesencephalic and bulbospinal animals.[2] They were readily demonstrated in chronic spinal cats.[13] In terms of the nontactile responses, all these preparations were identical except that the reactions were most pronounced in the spinal animals. No difference was observed in the intensity of responses exhibited by low cervical and low thoracic preparations. Since the stimulus-response relations of the two reactions are different, the characteristics of the spinal reflexes resulting from immersion in "hot" and in "cold" water will be discussed separately.

Immersion in "Cold" Water.—1. The movement produced was one of withdrawal, usually accomplished by flexion at the ankle, knee and hip, and typically followed by shaking movements of the paw, resembling an effort to rid the extremity of a noxious substance. At or near threshold, slight flexion, or merely a twitch, might be the only response elicited.

2. The reflexogenous zone extended from the toes to the knee, the most responsive area being the foot pad. Here the reaction could be elicited by stimulation of a punctate area. This was best done by directing a stream of ether or ethyl chloride on the foot pad through a fine hypodermic needle; the rapid evaporation of the compound resulted in cooling sufficient to evoke a response.

13. Macht, M. B.: A Hitherto Unreported Spinal Reflex in the Cat, Federation Proc. **3**:138, 1943.

3. The reaction time ranged from approximately one-half to four seconds. If a rubber stocking was placed around the paw, supplying additional thermal insulation, the reaction time could be lengthened to as much as eight seconds.

4. After withdrawal of the paw from the "cold" stimulus, shaking of the extremity might continue for as long as fifteen seconds.

5. The flexion response was accompanied with crossed extension of the opposite extremity.

6. Adaptation occurred rapidly. If the paw was forcibly held in cold water for approximately fifteen seconds and was then released and allowed to dangle in the water, no movement occurred. Such adaptation was observed (*a*) in water as low as O C., (*b*) when a piece of ice was pressed against the foot pad and (*c*) when ether was continuously sprayed on the foot.

7. That there is a relation between the temperature of the animal and the threshold for withdrawal of the paw is evident, but the exact nature of this relation is not entirely clear. It may be assumed that the temperature of the blood circulating in the paw closely approximates the rectal temperature. If this temperature is designated as x and the temperature of the water as y, then the minimum difference between x and y necessary to produce a response is an approximately linear function of x. However, the receptors for cold stimuli are situated close to the surface of the skin, and there is evidence that skin temperature is also related to threshold. If ether was sprayed on the foot pad for thirty seconds and the skin temperature of the pad lowered in this manner from an initial temperature of 34 C. to one of 22 C. (the rectal temperature remaining constant, at 37.5 C.), it was found that a lower temperature of the water was necessary to evoke the response of the paw on immersion, although the temperature of the blood circulating in the paw had been altered little, or not at all. Similarly, it will be noted in figure 2 that the temperature of water sufficiently low to elicit a response during the period when the body temperature was being raised was consistently higher than the threshold temperature of the water observed during the period when the body temperature was being lowered. It will be recalled that in the latter case the animal was in the cold chamber and the rectal (or blood) temperatures were always higher than the skin temperatures, while in the former case the animal was in the heating chamber under a battery of lamps and the skin temperatures were higher than the temperatures of the blood. Thus, it is apparent that skin temperature is in some manner related to the response. On the other hand, the reaction may occasionally be obtained when the skin temperature is equal to, or even a few degrees lower than, the temperature of the water.

The explanation of these seemingly confusing data is probably as follows: The temperature of water just low enough to evoke a reflex response is specifically related to the initial temperature of the receptors involved, to the temperature of the blood and to the skin temperature. The response is evoked when spatial thermal gradients are altered. When the foot pad is covered with a tough, thick callus, the temperature of the circulating blood more closely approximates the temperature of the receptors than does the surface skin temperature. Actually, the horny outer covering acts as thermal insulation, a fact which is demonstrated by the decrease in reaction time observed when such a callus is surgically removed from the foot pad.

Immersion in "Hot" Water.—1. The movement produced was one of withdrawal of the paw, similar to that described for immersion in "cold" water.

2. The reflexogenous zone extended from the toe pads to the knee, the most responsive area being the foot pad.

3. The reaction time ranged from approximately 0.5 to 8 seconds. The longer reaction times were observed at or near threshold and apparently were related to the relatively low temperature in the paw maintained by the circulating blood, additional time being required to heat the extremity sufficiently to stimulate the free nerve endings. The threshold could be lowered and the reaction time shortened by momentarily occluding venous return and, in this manner, permitting the temperature of the paw to rise more rapidly. A rubber stocking placed around the paw lengthened the reaction time but did not otherwise affect the response.

4. After withdrawal of the paw from the "hot" stimulus, shaking of the extremity sometimes continued for several seconds.

5. The flexion response was accompanied with cross extension.

6. Adaptation did not occur except at or near threshold.

7. The lowest temperature of water evoking a reaction bore no relation to the skin or blood temperature, except at or near threshold, when the circulating blood, tending, as it does, to maintain a constant receptor temperature, may slightly raise the threshold and the reaction time. The threshold stimulus is sufficiently high (approximately 50 C.) to produce a sensation of pain in the normal human subject.

STUDIES ON SPINAL MEN

To gain further information regarding the functional capacity of the human spinal cord, these studies were extended to spinal men. Unfortunately, one of the consequences of modern warfare is the production of men with complete transections of the cord; it was during World War I that Head and Riddoch[9] were able to conduct their classic investigation

of such patients. Since that time, advances in medical knowledge have greatly increased the longevity of spinal men and have gone far toward permitting them to regain a useful and relatively comfortable existence. Improved emergency measures in combating surgical shock, the use of sulfonamide compounds and antibiotics in the treatment of infection, new methods of dealing with dysfunction of the bladder and modern physiotherapeutic rehabilitation have contributed to this end. Such investigations as the present one are possible only because of the achievements of Munro[14] and other workers in the field.

MATERIAL AND PROCEDURE

Material.—A preliminary study of 6 men was conducted in 1942 at the Walter Reed Hospital, Washington, D. C. Neurologic examination of these subjects indicated that each had sustained a complete transection of the cord, but anatomic

TABLE 1.—*Levels of Transection of the Cord in the Patients Studied*

Levels of Transection, *Thoracic Segment	No. of Patients
3	2
4	1
5	4
6	5
7	2
8	3
9	2
10	3
12	2

verification was lacking. The results of tests conducted at that time, however, indicated that the isolated human spinal cord, like the cat's, is capable of mediating responses to thermal stimuli.

After a lapse of four years the investigation was resumed at the Cushing Veterans Administration Hospital, Framingham, Mass. Although many paraplegic patients were examined at this institution, the present paper is confined to a discussion of men with anatomically proved complete transection of the spinal cord. Men on whom rhizotomies had been performed were excluded. Twenty-four patients satisfying these criteria were studied. Levels of transection ranged from the third through the twelfth thoracic segments (table 1).

Twenty-two men were wounded by high velocity missiles, and 2 suffered compression fractures of the vertebral column with division of the cord. The nature and extent of injury were in each instance determined by exploratory laminectomy. The results of examination and a summary of the pertinent data are contained in table 2.

All these men were tested with thermal stimuli.

Methods.—The subjects were seated (and supported when necessary) on a bed or examining table, with the extremities hanging freely over the side. Whenever possible, the skin temperature of the foot was determined by means of no. 30

14. Munro, D.: Rehabilitation of Patients Totally Paralyzed Below the Waist, with Special Reference to Making Them Ambulatory and Capable of Earning a Living: I. Anterior Rhizotomy for Spastic Paraplegia, New England J. Med. **233**:453, 1945; II. Control of Urination, ibid. **234**:207, 1946; III. Tidal Drainage, Cystometry and Bladder Training, ibid. **236**:223, 1947.

Brown and Sharpe copper-constantan thermocouples and a Leeds and Northrup potentiometer. Water, at various temperatures, was used as the thermal stimulus. The containers employed were ordinary glass-walled aquariums, their transparency permitting accurate observation of the foot throughout the examination. Immersion was accomplished by slowly raising the vessel until contact was made with the foot. The extremity was carefully dried between tests, and when thresholds were being determined, five minutes was allowed to elapse between immersions in order to permit the skin temperature to reach equilibrium. The ambient temperature in all cases was 24 ± 1 C. The threshold for withdrawal from water above body temperature was designated as the lowest temperature of water from which the foot was withdrawn within ten seconds. The threshold for withdrawal from water below body temperature was designated as the highest temperature of water from which the foot was withdrawn within ten seconds. Motion pictures of the responses were taken to permit more accurate analysis.[15]

OBSERVATIONS

In spinal men, as in spinal cats, immersion of the lower extremities in water of body temperature produced no observed effect. Immersion of the foot in water of certain temperature levels above or below body temperature evoked responses which in many instances were similar to the reflexes described in animals.

Whereas the reaction pattern seen in all the cats tested was a stereotyped and readily predictable one, which varied little from animal to animal, pronounced qualitative and quantitative differences were noted in the responses of spinal men to thermal stimuli (figs. 3 and 4). This was true of maximal as well as threshold stimuli. The reflex pattern evoked in any particular subject by thermal stimulation was constant and, in general, was similar to the reaction produced in that subject by nociceptive stimulation of the same reflexogenous zone. The degree of response appeared to be roughly proportional to the activity of other spinal reflexes, particularly the tendon jerks. However, this was not always the case. For example, patient 2 (with section at the tenth thoracic segment) exhibited only a barely perceptible response to percussion of the patellar tendons, and the achilles reflex was completely absent bilaterally; yet his thermal responses were vigorous and dramatic (table 2). Extremely spastic patients always responded to thermal stimuli in a more exaggerated fashion than did subjects in whom spasms were less prominent.

Types of Response.—The most frequently observed response was one of triple flexion at the ankle, knee and hip, resulting in complete withdrawal of the extremity from the water. One muscle group usually acted predominantly. Thus, some subjects showed predominant flexion at the hip, so that the foot was lifted almost vertically from the water, whereas others responded principally with flexion at the knee, bending back the

15. Macht, M. B.: Autonomous Spinal Responses to Thermal Stimuli: A Study of Spinal Men, Federation Proc. **6**:161, 1947.

TABLE 2.—*Summary of Data Obtained in Examination of 24 Spinal Men—Continued*

Subject	Age, Yr.	Cause of Injury	Time Interval Since Injury, Days	Level of Lesion	Description of Lesion (Obtained at Exploration)	General Condition at Time of Examination	Tendon Reflexes	Thermal Responses (Rectal Temp.: 37.0-37.9C.) (Skin Temp.: 32-28 C.)		
								Threshold, Degrees C.		Type of Response
								"Cold"	"Hot"	
1	30	Shrapnel wound	822	T4-T5	Laminectomy (Feb. 1947) revealed complete transection of cord at T4-T5 and partial loss of cord substance at T3	Excellent; good nutrition; no catheter; little atrophy; severe spasms with strong adductor and extensor components	Knee jerk++++ bilaterally; sustained clonus Ankle jerk++++ bilaterally; sustained clonus	28	54	Response to cold: Strong, abrupt withdrawal of foot, accomplished by flexion at knee and hip, followed immediately by extensor spasm of both lower extremities Response to heat: Same as for cold but no extensor spasms at threshold. Not tested above 54C. for fear of injury
2	26	Shell fragment wound	939	T10	Laminectomy (June 1944) demonstrated complete transection of cord at level of T10	Excellent; remarkable muscular development of upper trunk, thorax and extremities; small ischial decubitus, reflex bladder	Slight knee jerk bilaterally Ankle jerk absent; no clonus	26	48	Response to cold: Vigorous withdrawal, with flexion at knee and hip; dorsiflexion of hallux Response to heat: Slight withdrawal at threshold; more marked at 52C., but not as vigorous as response to cold
3	28	Bullet wound	654	T4	Operative note, describing laminectomy (June 1945), stated "cord completely cut through at T4"	Excellent; good nutrition; patient ambulatory with braces; no catheter; reflex bladder	Knee jerk++++bilaterally Ankle jerk++++ bileterally; no clonus	27	49	Response to cold: Quick dorsiflexion of hallux with fanning of toes and flexion at thigh; no flexion at knee Response to heat: Dorsiflexion of hallux and fanning of toes at 50C.; no true withdrawal. Not tested at higher temperature for fear of injury
4	24	Bullet wound	738	T5	At exploratory laminectomy (August 1946) bullet removed from spinal cord, which was completely severed at T5	Excellent; patient ambulatory in braces; moderate bilateral atrophy of lower extremities; reflex bladder	Knee jerk+++bilaterally Ankle jerk++bilaterally; ankle clonus unsustained	27	48	Response to cold: Withdrawal accomplished by triple flexion, followed by extension at knee; dorsiflexion of hallux Response to heat: Short, sharp withdrawal similar to, but less marked than, response to cold. Not tested above threshold, however

Subject	Age, Yr.	Cause of Injury	Time Interval Since Injury, Days	Level of Lesion	Description of Lesion (Obtained at Exploration)	General Condition at Time of Examination	Tendon Reflexes	Thermal Responses (Rectal Temp.: 37.0-37.9C.) (Skin Temp.: 32-28 C.) Threshold, Degrees C. "Cold"	"Hot"	Type of Response
5	28	High explosive shell fragment wound	840	T6	Laminectomy (Dec. 3, 1946) demonstrated complete loss of spinal cord substance at T5; fibrous strand at this level was sectioned	Very poor; severe anemia; indwelling catheter, complete flaccidity and areflexia below lesion since injury; extreme atrophy of pelvis and lower extremities	Knee jerk absent Ankle jerk absent; no clonus	—	—	No response to thermal stimuli
6	26	Compression fracture sustained in parachute jump	1075	T6	Laminectomy (Dec. 23, 1946) revealed complete transection of cord at T6	Good condition; patient ambulatory with braces; no decubitus; indwelling catheter; tidal drainage	Knee jerk++ bilaterally Ankle jerk++bilaterally; no clonus	27	52	Response to cold: Vigorous withdrawal, accompanied by triple flexion at ankle, knee and hip Response to heat: Same as to cold
7	26	Bullet wound	883	T6	Laminectomy (Sept. 1944) demonstrated complete severance of spinal cord at level of T6	Good; no decubitus; indwelling catheter; atonic bladder, but no atrophy of lower extremities; completely flaccid and areflexic since injury	Completely absent	—	—	No response to thermal stimuli
8	24	High explosive shell fragment wound	649	T8	Laminectomy (April 1945) demonstrated complete absence of spinal cord for distance of 1.5 cm. immediately below lamina of T8	Excellent; good nutrition; no decubitus; moderate to severe spasms	Knee jerk++++ bilaterally Ankle jerk++++ bilaterally; sustained ankle clonus	24	48	Response to cold: Abrupt and vigorous dorsiflexion of hallux and foot with sharp flexion at knee Response to heat: Same as for cold, but less marked at threshold. Not tested at higher temperature
9	28	Injury from fall of 50 feet from airplane hangar	418	T9-T10	Laminectomy (Dec. 1945) demonstrated complete division of cord at T9-T10 and with 1 cm. gap between proximal and distal portion	Good; no decubitus; good nutrition; reflex bladder	Knee jerk++++ Ankle jerk++++; slight ankle clonus, unsustained	32	49	Response to cold: Strong triple flexion, resulting in withdrawal of entire limb Response to heat: Same as to cold

TABLE 2.—*Summary of Data Obtained in Examination of 24 Spinal Men—Continued*

Subject	Age, Yr.	Cause of Injury	Time Interval Since Injury, Days	Level of Lesion	Description of Lesion (Obtained at Exploration)	General Condition at Time of Examination	Tendon Reflexes	Thermal Responses (Rectal Temp.: 37.0-37.9C.) (Skin Temp.: 32-28 C.) Threshold, Degrees C. "Cold"	"Hot"	Type of Response
10	28	Shrapnel wound	616	T6	Laminectomy (July 1946) revealed complete transection of cord with cystic cavity 75x150 mm. at T5-T6 level	Good; small, shallow decubitus, right heel; chronic penoscrotal fistula	Knee jerk++++ bilaterally Ankle jerk+++ bilaterally; sustained ankle clonus	29	49	Reponse to cold: Vigorous flexion at hip and knee, followed frequently by strong extensor spasms of extremity stimulated and occasionally by extensor spasm bilaterally Response to heat: Same at 54C.
11	22	Bullet wound	950	T10	Laminectomy (Feb. 1947) demonstrated a huge bulging scar at midportion of body of tenth thoracic vertebra; cord fused to right lateral wall lere and immediately below this level cord completely absent for distance of 150 mm.	Excellent; small left trochanteric decubitus; tenth thoracic flexor spasms unless patient lies on abdomen	Knee jerk++++bilaterally; sustained clonus Ankle jerk++++bilaterally; sustained clonus	27	47.5	Response to cold: Vigorous flexion at ankle and hip, with leg lifting vertically from sitting position; response stronger on left Response to heat: Same, but less marked at threshold
12	20	Shell fragment wound	730	T5	Laminectomy (Jan. 1947) demonstrated proximal portion of cord ending at lower level of body of fourth thoracic vertebra and distal portion began at lower level of body of fifth thoracic vertebra	Good; no decubitus	Knee jerk+++bilaterally Ankle jerk++++bilaterally; sustained ankle clonus bilaterally	27	50	Response to cold: Strong extension of hallux with fanning of toes; slight flexion at knee and hip, followed by sustained ankle clonus Response to heat: Dorsiflexion of hallux and fanning of toes at 50C. Not tested at higher temperatures
13	34	High explosive shell fragment wound	810	T3-T4	Laminectomy (Nov. 1944) revealed "completely crushed and necrotic cord"	Excellent; no decubitus; strong spasms of lower extremities; reflex bladder; good nutrition	Ankle jerk+++bilaterally Knee jerk+++bilaterally; no clonus	29	50	Response to cold: Strong bilateral withdrawal with flexion at hip and knee, most marked at knee, the leg flexing far back and striking side of pail. Left foot also shows strong dorsiflexion with extreme dorsiflexion of hallux and fanning of toes Response to heat: Same as to cold

Subject	Age, Yr.	Cause of	Time Interval Since Injury, Days	Level of Lesion	Description of Lesion (Obtained at Exploration)	General Condition at Time of Examination	Tendon Reflexes	Thermal Responses (Rectal Temp.: 37.0-37.9C.) (Skin Temp.: 32-28 C.)		
								Threshold, Degrees C.		Type of Response
								"Cold"	"Hot"	
14	23	Shrapnel wound	952	T9	Laminectomy (Nov. 1944) demonstrated completely necrotic and severed cord at T9	Excellent; no decubitus; reflex bladder; patient ambulatory with braces	Knee jerk++ bilaterally Ankle jerk++bilaterally	25	50	Response to cold: Vigorous withdrawal with triple flexion at ankle, knee and hip Response to heat: Same as for cold, though less marked at threshold. Not tested above 50C.
15	23	High explosive shell fragment wound	763	T6	Laminectomy (Jan. 1945) showed spinal cord divided at T6	Good; no decubitus; reflex bladder; moderate spasms of lower extremities	Knee jerk++++ bilaterally Ankle jerk++++bilaterally; sustained ankle clonus bilaterally	30	49	Response to cold: Dramatic and vigorous, with ankle clonus, dorsiflexion of hallux, fanning of toes and sharp flexion at knee Response to heat: Dorsiflexion of hallux and fanning of toes at threshold. Not tested at higher temperature
16	27	Shrapnel wound	873	T5	Laminectomy (Sept. 25, 1945) revealed macerated cord at T5; two stumps excised in an attempt to alleviate intractable pain	Good; a few small scattered decubitus ulcers; slight edema of feet and ankles; no catheter	Ankle jerk+++bilaterally Knee jerk++bilaterally; slight ankle clonus, poorly sustained	28	50	At 20C. short, quick triple flexion at ankle, knee and hip with dorsiflexion of hallux sustained; no perceptible extensor or abductor component At 50C. response qualitatively similar to that at 20C, but less marked
17	26	High explosive shell fragment wound	845	T8	Exploratory laminectomy (Oct. 15, 1946) demonstrated complete transection of cord at T8	Excellent; no decubitus ulcers; severe spasms, both flexor and extensor of lower extremities; nutrition excellent	Knee jerk++++bilaterally; bilateral unsustained clonus Ankle jerk+++bilaterally; bilateral sustained clonus	29	48	Response to cold: Rapid, vigorous withdrawal, triple flexion at ankle, knee and hip with dorsiflexion of hallux Response to heat: Same, but less vigorous at temperature tested

TABLE 2.—*Summary of Data Obtained in Examination of 24 Spinal Men—Continued*

Subject	Age, Yr.	Cause of Injury	Time Interval Since Injury, Days	Level of Lesion	Description of Lesion (Obtained at Exploration)	General Condition at Time of Examination	Tendon Reflexes	Thermal Responses (Rectal Temp.: 37.0-37.9C.) (Skin Temp.: 32-28 C.) Threshold, Degrees C. "Cold"	"Hot"	Type of Response
18	22	Bullet wound	719	T3	Laminectomy (Dec. 5, 1946) demonstrated cystic cavity filled with fluid at T2; no neural elements present at this level	Excellent; no extensive atrophy; no catheter; superficial trochanteric decubitus	Knee jerk+++bilaterally Ankle jerk+++bilaterally; no clonus	18	—	Response to cold: Moderate triple flexion with mild dorsiflexion of hallux No response to temperatures between 18C and 50C. Not tested at higher temperatures for fear of injury
19	31	Gunshot wound	660	T8	Operative note (March 1945) stated, "Cord completely necrotic at T8."	Good nutrition; indwelling catheter; no marked atrophy; complete flaccidity and areflexia since injury	Completely absent	—	—	No response to thermal stimuli
20	34	High explosive shell fragment wound	730	T10	Exploratory operation (Jan. 1945) revealed complete transection of cord at level of T10; concomitant peripheral nerve injury with foot drop on left	Excellent, but patient has severe spasms, necessitating lashing to bed and prohibiting use of braces	Knee jerk+; left trace Ankle jerk absent	22	53	Response to cold: Left: slight twitch of hallux. Right: Strong extension of hallux and fanning of toes with extension of foot Response to heat (53C.): Responses same as those to cold
21	32	Shrapnel wound	936	T12	Laminectomy (Aug. 1944) demonstrated large cavity at T12, invading one-half body of vertebra and connecting directly with spinal cord; cord absent between T11 and T12	Excellent; no decubitus ulcers	Knee jerk absent bilaterally; percussion of left patella results in downward movement of foot Ankle jerk+++++bilaterally; bilateral sustained clonus	24	52	Response to cold: Immersion of one extremity results in bilateral abduction of entire lower extremities, movement being mainly at hips, although there is also slight eversion of feet (adduction at ankles); response equal bilaterally on immersion of one extremity Response to heat: Same as that to cold
22	20	High explosive shell fragment wound	1104	T12	Laminectomy (Feb. 1944) demonstrated bullet tract completely severing cord at level of T12	Excellent; reflex bladder; no decubitus; fair nutrition	Knee jerk+++ Ankle jerk+; no clonus	28	50	Response to cold: Slight triple flexion at ankle, knee and hip; dorsiflexion of hallux Response to heat: Same, but less marked at threshold

Subject	Age, Yr.	Cause of Injury	Time Interval Since Injury, Days	Level of Lesion	Description of Lesion (Obtained at Exploration)	General Condition at Time of Examination	Tendon Reflexes	Thermal Responses (Rectal Temp.: 37.0-37.9C.) (Skin Temp.: 32-28 C.)		
								Threshold, Degrees C.		Type of Response
								"Cold"	"Hot"	
23	27	Machine gun bullet wound	969	T7	Laminectomy disclosed "completely crushed and necrotic spinal cord" at level of T7; complete flaccidity since injury; direct electrical stimulation of sciatic nerve produced no response whatever	Fair: left ischial decubitus; advanced bilateral atrophy of lower extremities; indwelling catheter	Completely absent	—	—	No response to thermal stimuli
24	23	High explosive shell fragment wound	583	T7	Laminectomy (Aug. 1946) revealed scar 4 cm. in length at T6-T8, with shell fragment 3x3x5 cm. in center; on removal complete break in continuity of cord apparent	Excellent; good nutrition; moderate atrophy of gastrocnemius bilaterally; trochanteric decubitus ulcers bilaterally; strong flexor spasms bilaterally	Knee jerk++++bilaterally Ankle jerk++++bilaterally; ankle clonus sustained	28	47.5	Response to cold: Sudden, sharp triple flexion with dorsiflexion of hallux and fanning, followed by intense and continued flexor spasm Response to heat: Same as that to cold, though less marked at threshold

leg on the thigh. Triple flexion was usually accompanied with adduction of the extremity involved, although occasionally the opposing movement of abduction occurred. In many cases stimulation of one extremity resulted in a bilateral movement but the flexion-crossed extension response

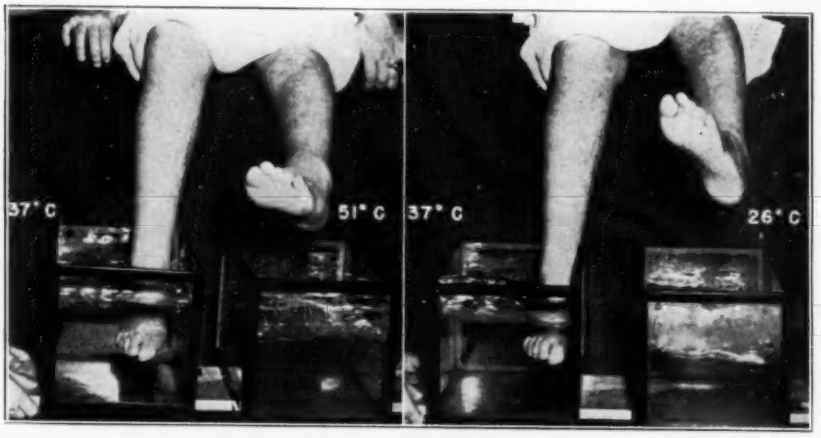


Fig. 3.—Withdrawal responses from "hot" and "cold" water, with strong extensor component, in a man with transection of the spinal cord at the sixth thoracic segment.

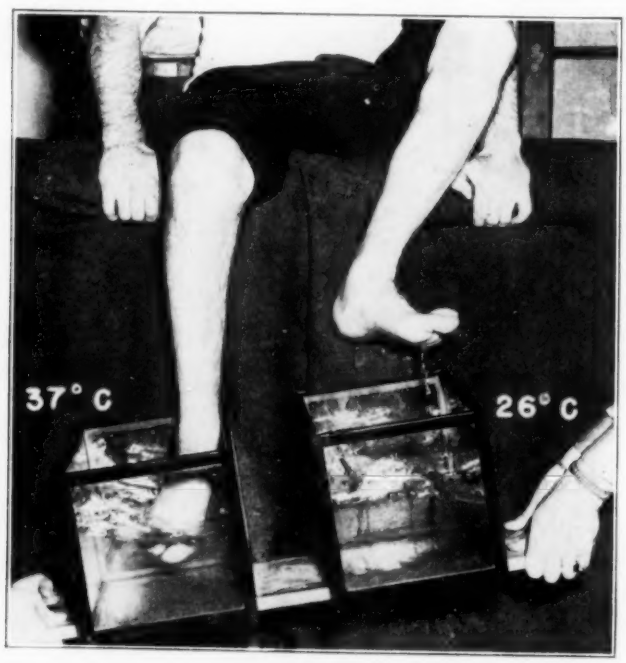


Fig. 4.—Withdrawal response from "cold" water in a man with transection of the spinal cord between the third and the fourth thoracic segment. The movement is primarily flexor.

was not observed typically Two men showed only dorsiflexion of the hallux and fanning of the toes to thermal stimulation. One patient exhibited only bilateral adduction at the hip.

Although the withdrawal movement is primarily one of flexion, various combinations of flexion and extension were observed in spastic persons. In this group of patients the flexion withdrawal movement was frequently followed by marked extensor or flexor spasms, lasting several minutes and sometimes accompanied with spinal sweating. In these cases, thermal stimulation undoubtedly evoked a form of mass reflex.

When responses occurred, they were qualitatively the same for both "cold" and "hot" stimuli. However, in order to avoid the risk of injury, men were rarely tested above threshold with "hot" stimuli. For this reason, the responses observed for heat were, in general, much weaker than the maximal responses to cold. No relation was observed between the level of section of the cord (third to twelfth thoracic) segment and the type or degree of response.

Four subjects showed no response to thermal stimuli. These men were interesting because none of them had ever demonstrated any spinal reflexes since injury. Their bladders were atonic and their tendon reflexes were absent. To all intents and purposes, they were still in spinal shock, although in each transection had occurred between two and three years previously. Two of these men (cases 5 and 23) were in poor general condition and displayed advanced atrophy of the lower extremities. However, the other 2 men (cases 7 and 19) were in excellent condition, with little or no atrophy below the level of section. Whether these men were in true spinal shock or whether they represented, in man, the state of isolation dystrophy described by Sherrington in spinal animals,[16] was not possible to determine.

One of these patients (case 23) presented a unique opportunity for an examination of peripheral nerve function in one lower extremity. This man had a deep and troublesome decubitus ulcer in the left ischial region, which required surgical intervention. At operation, the left sciatic nerve was exposed and was stimulated faradically by both surface contact of the electrodes with and their insertion into the nerve trunk. No response whatever could be evoked by such stimulation, although the nerve did not look in any way abnormal.

Thresholds for Thermal Responses.—For several reasons, complete studies of threshold stimuli for these men could not be conducted. All the subjects were volunteers, and care was taken to avoid any injury or discomfort. Because they fatigued easily, it was feasible to work with

16. Sherrington, C. S.: Experiments in Examination of the Peripheral Distribution of the Fibres of the Posterior Roots of Some Spinal Nerves (Croonian Lecture), Phil. Tr. **190B**:45, 1898.

them only for short periods at a time. Unlike mesencephalic cats, whose body temperatures can easily be raised or lowered, it is rather difficult to alter the internal temperature of the foot of a spinal man. It would have been desirable to have made subcutaneous temperature measurements of the foot, but permission for such procedures could not be obtained. For these and other reasons, certain of our conclusions regarding threshold stimuli are, of necessity, based on inferential reasoning and on evidence obtained in animal experiments.

Threshold for Response to "Cold" Stimuli.—Initial skin temperatures ranged from 32 to 28 C. (89.6 to 82.4 F.); little or no correlation between the threshold temperature of the water and skin temperatures was observed within this range. The threshold "cold" stimulus varied from 18 to 32 C. (64.4 to 89.6 F.). The mean threshold "cold" stimulus was a water temperature of 26.8 ± 3.1 C. For 15 of the 20 men in whom thermal responses could be evoked, thresholds were between 25 and 30 C. (77 and 86 F.). For these subjects, the average difference between skin temperatures and water temperatures was 4 ± 0.2 C. The threshold stimulus for 2 men was 24 C. (75.2 F.), and for each of 3 subjects they were 18, 22 and 32 C. (64.4, 71.6 and 80.6 F.), respectively. The threshold for any single subject was fairly constant under similar conditions, and the readings on repeated examinations of the same subject usually checked within 1 degree C.

Various procedures were carried out in an attempt to modify the threshold for "cold." Prior immersion of an extremity for ten minutes in water considerably above body temperature resulted in a change of threshold in 6 of 7 subjects so tested.

Dec. 2. 1946 (case 13): Transection between the third and fourth thoracic segments. Initial skin temperature, 30 C. (86 F.). Ambient temperature, 24 C. (75.2 F.). Threshold "cold" stimulus, immersion in water at 28 C. (82.4 F.). No response at 29 C. (84.2 F.). Extremity immersed in water at 46 C. (114.8 F.) for fifteen minutes ("hot" threshold, 49 C. [120.2 F.]). Skin temperature after immersion 42 C. (107.6 F.). Subsequent immersion in water at 32 C. (89.6 F.) produced withdrawal response.

In an effort to raise rapidly the internal temperature, as well as the skin temperature, of the foot, the venous return was occluded for fifteen minutes in 5 subjects by the inflation of a sphygmomanometer cuff about the lower part of the leg, with pressure maintained at 80 mm. of mercury. No change in the threshold of response to "cold" stimulus was observed. Arterial occlusion of the lower extremity, however, produced a profound effect on the response to "cold" exhibited by 5 subjects so tested. This is illustrated by the protocol of an experiment performed in case 10 on Feb. 12, 1947 (transection between the fifth and sixth thoracic segments).

10:15 a.m.: Room temperature, 24 C. (75.2 F.)
Rectal temperature, 37.2 C. (98.96 F.)
Blood pressure, 136 systolic and 74 diastolic
Initial skin temperature of foot, 29 C. (84.2 F.)
Initial threshold for response to "cold": water at 27 C. (80.6 F.)
Initial threshold for response to "heat": water at 50 C. (122 F.)
10:20 a.m.: Sphygmomanometer cuff inflated about leg 15 cm. above ankle; pressure maintained at 200 mm. of mercury
Foot immersed in water bath at 29 C.
10:30 a.m.: Skin temperature of foot, 29 C.
Water bath removed; foot cyanotic
Foot dried and threshold tested
Threshold for "cold": water at 26 C. (78.8 F.)
Threshold for "heat": water at 50 C.
Foot replaced in water bath
10:36 a.m.: Skin temperature of foot, 29 C.
Water bath removed; foot cyanotic
Foot dried and thresholds tested
Threshold for "cold": water at 26 C.
Threshold for "heat": water at 50 C.
Foot replaced in water bath
10:43 a.m.: Skin temperature of foot, 29 C.
Threshold for "cold": 20 C. (68 F.)
Threshold for "heat": 49 C. (123.8 F.)
Foot replaced in water bath
10:55 a.m.: Skin temperature of foot, 29 C.
Threshold for "cold": water at 16 C. (60.8 F.)
Threshold for "heat": water at 49 C.
Foot replaced in water bath
11:05 a.m.: Skin temperature of foot 29 C.
Threshold for "cold": water at 14 C. (57.2 F.)
Threshold for "heat": water at 50 C.
11:06 a.m.: Sphygmomanometer cuff removed
11:17 a.m.: Leg and foot hyperemic below level of cuff
Skin temperature of foot, 30 C. (86 F.)
Threshold for "cold": water at 28 C. (82.4 F.)
Threshold for "heat": water at 50 C.

These observations are in striking agreement with the studies of Clark, Hughes and Gasser[17] regarding the effects of pressure block on conduction in the saphenous nerve of the cat and with the experiments of Lewis, Pickering and Rothschild[18] on the differential loss of sensation produced in normal human subjects by arterial occlusion of an extremity.

Forced immersion of the extremity in ice water for ten minutes profoundly modified the threshold for the response to "cold," evidently as

17. Clark, D.; Hughes, J., and Gasser, H. S.: Afferent Function in the Group of Nerve Fibres of Slowest Conduction Velocity, Am. J. Physiol. **114**:69, 1935.

18. Lewis, T.; Pickering, G. W., and Rothschild, P.: Centripetal Paralysis Arising out of Arrested Blood Flow to the Limb, Including Notes on Form of Tingling, Heart **16**:1, 1931.

a result of adaptation. Such a procedure resulted in complete abolition of the reflex to "cold" stimulation for a period of thirty to sixty seconds, and subsequent immersion, three to five minutes after this time, revealed that a much lower temperature of water was required for a threshold response.

Thresholds for Response to "Hot" Stimuli.—The threshold stimulus for withdrawal from water above body temperature varied from 47.5 to 54 C. (117.5 to 129.2 F.). In general, examinations at temperatures higher than threshold were not performed for fear of causing injury. One subject (case 18), who exhibited a response to immersion in "cold" water, showed no response to water at 50 C. and was not tested at higher temperatures.

The mean threshold stimulus for the response to "hot" stimuli was a water temperature of 49.7 ± 1.8 C. As in the case of "cold" stimuli, the threshold for any one subject was constant. Moreover, the only modification in threshold was obtained when venous return was occluded by the application of a cuff to the lower part of the leg. In 6 of 7 men so tested, this procedure resulted in a lowering of the threshold by 1 or 2 degrees, (C.), probably because it was no longer possible for the circulating blood to cool the foot sufficiently to prevent stimulation of free nerve endings.

Arterial occlusion for forty minutes produced no appreciable effects on the response to heat.

Prior immersion of the foot in ice water had no effect on the threshold but increased the reaction time.

No adaptation was observed except at or near threshold.

COMMENT

It is somewhat surprising that these vigorous and striking responses to thermal stimuli have not been described by previous investigators. Sherrington and Laslett,[5] in 1903, immersed spinal animals in ice water, but they did not mention any specific reflex movements evoked by this procedure. Absence of such a response is probably best explained by the adaptation of the receptors to the cold stimulus. As previously stated, such adaptation occurs rapidly, and after a short period of immersion the limbs become unresponsive. Any flexion responses exhibited initially by their animals may have been interpreted by Sherrington and Laslett as the "mark time" reflex, or as spontaneous running movements. Sherrington[11] did report flexion reflexes in response to "injurious heat" and attributed them, as we do also, to stimulation of receptors which normally subserve the sensation of pain. Bazett and Penfield[19] kept their

19. Bazett, H. C., and Penfield, W. G.: A Study of the Sherrington Decerebrate Animal in the Chronic as Well as the Acute Condition, Brain 45:185, 1922.

decerebrate cats immersed in water, but in this case it is not surprising that no reactions were observed, since the water was always thermostatically controlled at 37 C. It is interesting that many of the paraplegic subjects examined in these experiments volunteered the information that they had observed movements of their lower extremities when taking a cold bath or when cold water was inadvertently splashed on a foot.

Analysis of sensation or any subjective reactions in animals is impossible, for, by definition, a subjective impression is one which in order to be known by others must be reported by the subject himself. Thus, the subject must be able to verbalize, and the afferent impulses must travel from the receptors to the cerebral cortex in order to be perceived and reported. These criteria, obviously, cannot be fulfilled in spinal men when the receptors stimulated are innervated by the isolated cord. It follows, therefore, that any conclusions regarding the modalities of sensation involved in these responses must be based on inferential reasoning.

Endres,[20] and Bazett, McGlone and associates,[21] among others, verified the theory of the dependence of cold sensations on Krause's end organs, as originally suggested by von Frey.[22] The manner in which temperature sensations are induced, however, is the subject of considerable controversy. We are in agreement with Ebbecke's[23] classic hypothesis that temperature sensations occur when spatial thermal gradients are altered ("A sensation of cold is produced when warm blood streams into cold skin"). A modification of this theory, proposed by Bazett and McGlone,[24] is that induction of thermal sensation occurs as the result of either cooling or warming of the blood, or both, if this happens in the neighborhood of the end organ, whether the alteration in temperature resulted from a change in temperature of the tissue as a whole or from the flow of blood across a thermal gradient. This would readily explain adaptation to cold, for, as the lowered temperature progressed inward, the blood would be

20. Endres, G.: Punktionsnarkose von Rezeptoren, Ztschr. f. Biol. **89**:536, 1930.

21. Bazett, H. C.; McGlone, B.; Williams, R. G., and Lufkin, H. M.: Studies in Sensation: I. Depth, Distribution and Probable Identification in the Prepuce of Sensory End-Organs Concerned in Sensations of Temperature and Touch, with Observations on Thermometric Conductivity in the Prepuce, Arch. Neurol. & Psychiat. **27**:489 (March) 1932.

22. von Frey, M.: Beiträge zur Sinnesphysiologie der Haut, Ber. u. d. Verhandl. d. Kong. Sachs. Gesellsch. d. Wissensch. **2**:166, 1895.

23. Ebbecke, U.: Ueber die Temperaturempfindungen in ihrer Abhängigkeit von der Hautdurchblutung und von den Reflexzentren, Arch. f. d. ges. Physiol. **169**:395, 1917.

24. Bazett, H. C., and McGlone, B.: Studies in Sensation: II. Mode of Stimulation of Cutaneous Sensations of Cold and Warmth, Arch. Neurol. & Psychiat. **27**:1031 (May) 1932; III. Chemical Factor in Stimulation of End-Organ Giving Temperature Sensations, ibid. **28**:71 (July) 1932.

cooled before reaching the end organ, and neither strong thermal gradients nor local cooling of blood would be much in evidence.

The responses of spinal animals and spinal men to immersion in "cold" water appear to be in accordance with this theory, and our experimental results indicate that the receptors involved are Krause's end organs. In other words, the effective stimulus is one of cold rather than of pain. The evidence for this view is as follows:

1. Normal human controls with blood and skin temperatures identical with those of spinal subjects report that water at a sufficiently low temperature to evoke a withdrawal response in spinal men feels "cool," "slightly cold" or "cold," but never "painful."

2. Poikilothermic animals exhibit a linear relation between rectal (and presumably blood) temperature and threshold of response. The threshold in spinal men can be modified by prior immersion of the extremity in water of very high (45 C. [113 F.]) or very low 5 C. [41 F.]) temperature.

3. Arterial occlusion of an extremity results in modification of the threshold for withdrawal from water below body temperature in a manner which sugests that the modality of sensation involved is cold.

Gasser and Erlanger,[25] whose fundamental work on the specificity of afferent nerve fibers has yielded results of far reaching importance, studied the compound action potential of mixed nerve trunks. They concluded that (*a*) the velocities of fibers vary directly with their diameters and (*b*) the potentials in the fibers affect a potential-recording devise in proportion to their cross sectional areas. Clark, Hughes and Gasser[17] studied the order in which the different fibers of the saphenous nerve of the cat were blocked when a pressure cuff, placed around the leg of the animal, occluded the arterial inflow. The results of their experiments complemented dramatically the findings of Lewis, Pickering and Rothschild,[18] who studied similar asphyxial blocks in human subjects.

> The time relations of the loss of sensation in man furnish a striking parallel to the time relations of the changes in the electroneurogram of the cat's saphenous under analogous conditions. For the first 15 minutes, in the human experiment, no loss of sensation occurs. During a similar period the electroneurogram of the cat's saphenous shows no change except a slight slowing of conduction rates. In man, the sensations of touch, pressure, vibrations, and position begin to disappear rapidly after about 15 to 20 minutes, and the sensation of cold begins to go at about the same time or slightly later. In the cat, there is rapid disappearance of the "A" and "B" elevations during this period. After 30 to 45 minutes the human

25. Gasser, H. S.: Conduction in Nerves in Relation to Fiber Types, A. Research Nerv. & Ment. Dis., Proc. **15**:35, 1935. Gasser, H. S., and Erlanger, J.: The Role Played by the Sizes of the Constituent Fibers of a Nerve Trunk in Determining the Form of Its Action Potential Wave, Am. J. Physiol. **80**:522, 1926.

subject has completely lost the sensations named above and the only responses obtainable from the area distal to the cuff by any sort of intensity of stimulus are delayed sensations of warmth and of a severe burning pain. In the cat's saphenous at this time all "A" and "B" fiber activity has been lost and the "C" fibers alone are conducting impulses through the asphyxiated region. After release of the cuff the sensations in man and the electroneurogram in the cat return in a few minutes to the normal state.[17]

In the light of these studies, our results with arterial occlusion of the lower extremities of spinal men afford suggestive evidence regarding the modalities of sensory stimulation involved in evoking the withdrawal response. Arterial occlusion for twenty to thirty minutes strongly affects the threshold for withdrawal from "cold" water. After thirty minutes, the response to "cold" water is virtually absent, and, apparently, a "cold-pain" stimulus is required to obtain the reaction. The threshold for "hot" stimuli, on the other hand, is not altered to an appreciable extent. Within five minutes after the pressure has been released, the threshold for "cold" stimulus returns to its original level.

4. The rapid adaptation to the stimulus is typical of thermal receptors and occurs more rapidly and completely than would be expected of pain receptors.[26] The responses to immersion in "hot" water appear to be due not to stimulation of the receptors for warmth, or end organs of Ruffini, but to stimulation of pain receptors, or free nerve endings. The evidence for this view is as follows:

1. Normal human controls with similar blood and skin temperatures report that water of a temperature sufficiently high to evoke a withdrawal response in spinal men feels "painful" or "extremely hot," but not merely "warm."

2. There is no relation between body or skin temperature and threshold, nor can the threshold be modified by prior immersion in hot or cold water. Thus, it would appear that the induction of an absolute temperature of approximately 50 C. is required to elicit the reflex. This is not entirely in agreement with the concept of thermal pain advanced by Fujita[27] and Lewis and Hess[28] that the duration of the gradient also contributes to the production of such pain.

3. Adaptation does not occur except at or very near threshold.

---

26. Tower, S. C.: Nerve Impulses from Receptors in the Cornea, Proc. Soc. Exper. Biol. & Med. **32**:590, 1935. Heinbecker, P.; Bishop, G. H., and O'Leary, J. L.: Pain and Touch Fibers in Peripheral Nerves, Arch. Neurol. & Psychiat. **29**:771 (April 1933; Analysis of Sensation in Terms of the Nerve Impulse, ibid. **31**:34 (Jan.) 1934.

27. Fujita, T.: Einige weitere Erfahrungen über den Hitzeschmerz, Jap. J. M. Sc. III, Biophysics **3**:101 (Sept.) 1934.

28. Lewis, T., and Hess, W.: Pain Derived from Skin and Mechanism of Its Production, Clin. Sc. **1**:39, 1933.

4. Pressure block for thirty to forty minutes has no appreciable effect on the response.

The withdrawal responses to both "hot" and "cold" stimuli are similar to other protective flexion reflexes exhibited by spinal subjects. However, the shaking movements made by the spinal cat after withdrawal appear to be reactions to the fluid medium and are identical with those seen when the paw of a normal animal touches water.

It is probable that all three of the withdrawal responses evocable in the cat, which are produced by tactile, cold and pain stimuli, respectively, also obtain in human beings. One hundred full term infants and 17 premature infants, examined shortly after birth, responded to immersion of the foot in a manner similar to that of spinal subjects. These babies displayed responses to "cold" or "hot" water but not to water of body temperature. On the other hand, blindfolded older children (5 to 7 years of age) withdrew the foot from water of any temperature.[29]

SUMMARY

Data obtained in a study of 41 cats and 24 spinal men indicate that the isolated spinal cord in both cat and man is capable of mediating responses to thermal stimuli.

In the normal cat a withdrawal response, evoked by tactile stimuli and dependent on the functional integrity of the frontal poles of the cerebral cortex, masks two purely spinal reflexes.

All three reflexes are of the protective flexion type. The responses to nontactile stimuli of decorticate, mesencephalic, bulbospinal and spinal cats are identical, though these reactions are most pronounced in the spinal preparation.

Evidence indicates that the withdrawal response evoked by immersion in "cold" water is produced by stimulation of Krause's end bulbs and that the sensory modality involved is *cold*.

The response evoked by immersion in "hot" water is independent of skin or blood temperature and is apparently produced by stimulation of free nerve endings. The sensory modality involved is probably *pain*.

Twenty of 24 men with anatomically proved complete transections of the thoracic portion of the spinal cord (third to twelfth segment) exhibited similar responses to thermal stimuli. The level of transection was not found to be related to strength, type or threshold of response.

The 4 subjects who showed no reaction to thermal stimuli had never exhibited spinal reflexes of any kind since injury.

Department of Physiology, Johns Hopkins University School of Medicine.

29. Macht, M. B.: Responses of Infants and Older Children to Thermal Stimuli, to be published.

TRYPAN RED THERAPY OF AMYOTROPHIC LATERAL SCLEROSIS

Preliminary Report

ROBERT B. AIRD, M.D.
SAN FRANCISCO

PREVIOUS STUDIES on the supravital dyes vital red (c.i. no. 456; brilliant vital red)[1] and trypan red (c.i. no. 438)[2] have shown that these acid dyes lower the permeability of the blood-cerebrospinal fluid barrier and the blood-brain barrier for various test agents, such as cocaine and triphenylphosphite. This effect is associated with the protective action of the dyes in both experimental epilepsy and human convulsive states. The effect of vital red was demonstrated by the fact that it afforded protection against various epileptogenous agents, and by direct spectrophotometric determinations, which showed that it lowered the permeability of the blood-cerebrospinal fluid barrier to cocaine hydrochloride. Since it was found that the supravital dye had no central effect on the central nervous system, and no peripheral effect in neutralizing or combining with the convulsive agents, it was postulated that the action of the dye on the blood-brain barrier was similar to its measured effect on the blood-cerebrospinal fluid barrier. The fact that vital red is an acid dye and stains intensely the endothelium of both the blood cerebrospinal fluid barrier and the blood-brain barrier further contributed to this conclusion. Direct evidence of the effect of the dye on the blood-brain barrier, however, was lacking.

Trypan red, a supravital diazo dye closely related to vital red, was found to parallel the latter in its staining properties and its physiologic effect in affording protection against cocaine used as an epileptogenous agent in experimental epilepsy. The distribution of cocaine in the motor cortex, the cerebrospinal fluid and the blood of cats was accurately determined by spectrochemical methods under standard conditions.

From the Division of Neurology, University of California Medical School.

This work was supported by the Christine Breon Fund for Medical Research.

1. Aird, R. B.: The Mode of Action of Brilliant Vital Red in Epilepsy, Arch. Neurol. & Psychiat. **42**:700-723 (Oct.) 1939.

2. Aird, R. B., and Strait, L.: Protective Barriers of the Central Nervous System: An Experimental Study with Trypan Red, Arch. Neurol. & Psychiat. 51:54-66 (Jan.) 1944.

When similar groups of cats were given injections of trypan red, the amount of cocaine entering the cortex and cerebrospinal fluid was lowered by about 30 per cent or more, while the concentration in the blood remained essentially the same. The alteration of the permeability of both the blood-brain and the blood-cerebrospinal fluid barrier by trypan red was thus established by direct methods.

An obvious implication of these studies was the possible therapeutic value of the dyes in toxic and degenerative diseases of the central nervous system. It was conceivable that the vital dyes might protect against toxic diseases of the central nervous system, such as retrobulbar neuritis, eclampsia and lead encephalopathy, as well as against toxic convulsive states. Cobb and associates[3] found that vital red protected against triphenylphosphite used as a convulsive agent. Studies by my associates and me[4] verified this observation, and, in addition, indicated that triphenylphosphite was quickly hydrolyzed after its injection and that two distinct effects could be ascribed to its breakdown products. The phenol fraction produced early convulsive effects at the level of the cord, while the phosphorous acid fraction caused a delayed degeneration in the cord and brain stem.[5] This suggested that the supravital dyes might have therapeutic value in degenerative diseases of the central nervous system of possible toxic origin. The systematic trial of the therapeutic value of these agents in degenerative diseases of the central nervous system of possible toxic origin, such as amyotrophic lateral sclerosis, as well as in toxic conditions of the central nervous system, thus appeared to be justified. The present report is a preliminary account of our experiences over the past seven years with the use of these dyes in 12 cases of amyotrophic lateral sclerosis.

METHOD

The clinical diagnosis was established in each patient after a thorough study and was independently verified by one or more neurologists other than me. Roentgenograms of the cervical portions of the spine were taken to rule out the rare possibility of cervical lesions associated with conditions simulating amyotrophic lateral sclerosis.[6] Myograms and motion pictures of involved muscles were obtained

3. Cobb, S.; Cohen, M. E., and Ney, J.: Brilliant Vital Red as an Anticonvulsant, J. Nerv. & Ment. Dis. **85**:438-441 (April) 1937; Anticonvulsive Action of Vital Dyes, Arch. Neurol. & Psychiat. **40**:1156-1177 (Dec.) 1938.

4. Aird, R. B.; Cohen, W. E., and Weiss, S.: Convulsive Action of Triphenyl Phosphite, Proc. Soc. Exper. Biol. & Med. **45**:306-309 (Oct.) 1940.

5. Smith, M. I.; Lillie, R. D.; Elvove, E., and Stohlmann, E. F.: Pharmacologic Action of Phosphorus Acid Esters of Phenols, J. Pharmacol. & Exper. Therap. **49**:78-99 (Sept.) 1933.

6. Fay, T.: High Cervical Laminectomy in Three Cases of Amyotrophic Lateral Sclerosis, Tr. Am. Neurol. A. **68**:63-66, 1942.

in most instances, and additional ones were made when possible for purposes of an objective follow-up study.

One per cent solutions of vital red and trypan red were prepared with triple-distilled water. The solutions were sterilized after Seitz filtration and injected intravenously with the usual aseptic technic. In most instances 20 cc. of vital red was injected daily for five days, making a total dose of 100 cc. Daily injections of 10 cc. of trypan red were then given for from five to eight days, followed by similar injections every second day for three or four doses and every three or more days thereafter up to a total dose of 25 mg. per kilogram of body weight. Urinalyses for albumin, cells and casts were made frequently in the late stages of the injections, to guard against any toxic effect of the dyes on the kidneys. Injections were given at slower intervals if the patient reported more than a trace of dye in the urine. The course of injections required from four to five weeks and resulted in a brilliant staining of the skin and conjunctival vessels. The scleras were stained a light pink. The dyes were excreted chiefly via the intestine, and secondarily by the sweat glands and the nasal and oral secretions.

No immediate or late toxic effects were observed in this series other than occasional, transient photophobia and blurring of vision. No changes were found on ophthalmologic examination in these cases, and the condition invariably cleared over a period of from one to three weeks. Nonuse of the eyes and wearing of dark glasses materially added to the comfort of the occasional patients so afflicted. The use of vitamin A in high doses (25,000 units per day) was thought to benefit these patients and has also been used prophylactically for all the patients treated in the last four years.

Although our experience with the dye therapy of amyotrophic lateral sclerosis is now more extensive, this report is limited to the 12 cases in which we have been able to maintain contact and obtain a good follow-up over a period of at least two years.

RESULTS

The salient factors in the 12 cases of amyotrophic lateral sclerosis studied in this series are presented in the accompanying tables, along with the results obtained with the dye therapy. In an attempt to facilitate an evaluation of the treatment, the results were arbitrarily classified on the following basis:

Classification	Results of Dye Treatment
0	No objective improvement; possible subjective improvement
1	Diminished fasciculation; subjective improvement
2	Diminished fasciculation; subjective improvement; suggestive slowing of disease process (wasting and weakness)
3	Process arrested; possible improvement in strength and weight

In 3 cases there was no change, and in 4 cases diminished fasciculation was the only result of treatment. The disease process was suggestively modified in 3 cases and appeared to be arrested in 2 cases.

Illustrative case reports of classifications 2 and 3 are given to indicate in more detail the type of neurologic alterations observed in some of the cases.

CASE 10 (classification 2).—M. L., a housewife aged 35, first noted "plucking sensations" in the left arm and weakness of extension of the fingers of the left hand in June 1941. The weakness progressed; movements of the left hand became clumsy, and obvious fasciculation and atrophy of the muscles of the left

Clinical Data and Effect of Dye Therapy in 12 Cases of Amyotrophic Lateral Sclerosis

Condition When Treatment Started							Effect of Treatment					
Case	Sex	Age	Duration of Symptoms (Mo.)	Severity	Rate of Progress*	Complications	Fasciculations	Weakness and Wasting of Muscles	Reflexes	Speech and Swallowing	Period of Observation (Mo.)	Classification† Results
1	M	70	24	Advanced	Rapid		Progressive	Progressive	Same	Progressively worse	2 (died)	0
2	M	30	6	Advanced	Rapid	Diabetes mellitus	Progressive	Progressive	Same	Progressively worse	5 (died)	0
3	M	45	48	Advanced	Rapid		Progressive	Progressive	Same	Progressively worse	10 (died)	0
4	M	54	6	Moderate	Rapid		Diminished	Transient improvement	Same	Progressively worse	12 (died)	1
5	M	53	6	Moderate	Rapid	High blood pressure, asthma	Diminished	Transient improvement	Same	Progressively worse	12 (died)	1
6	M	41	5	Moderate	Rapid		Diminished	Transient improvement	Same	Not involved	19 (died)	1
7	M	40	8	Moderate	Rapid		Diminished	Transient improvement	Same	Progressively worse	35 (to date)	1
8	M	39	11	Slight	Moderate		Diminished	Very slow progression	Same	Not involved	24 (to date)	2
9	M	36	16	Advanced	Rapid		Diminished	Very slow progression	Same	Slow progression	28 (died)	2
10	F	35	18	Moderate	Moderate		Diminished	Very slow progression	Same	Slow progression	57 (to date)	2
11	M	34	30	Moderate	Moderate		Arrested	Weakness improved; wasting arrested	Returned to normal	Not involved	36 (to date)	3
12	F	20	36	Slight	Moderate		Arrested	Arrested	Returned to normal	No change	81 (to date)	3

*Rate of progress at time of study and treatment.
†See text for an explanation of the classifications

hand developed over the next few months. Similar changes had appeared in the right hand by July 1942. At about the same time she first noted dragging of the left leg and some stiffness and weakness of both legs in climbing. Sensory symptoms, probably secondary to the extensive changes in the motor system, consisted of questionable hypersensitivity in the arms, some muscular cramping and aching in the left arm, occasional slight pains in the left side of the neck and a dull, ill defined ache in the frontal and occipital regions. Slurring of speech and some impairment of emotional control had been noted in the fall of 1942.

Examination.—On admission to the hospital, in November 1942, the patient was slightly obese, weighing 65 Kg., and was cooperative and intelligent. Slight slurring of speech was detectable. Moderate wasting of the muscles of both forearms and more advanced atrophy of the intrinsic muscles of the hands were associated with corresponding weakness and fascicular twitchings. The left hand and forearm showed these changes more prominently than the right. The fingers were slightly flexed in a manner suggestive of the ulnar claw hand, or *main en griffe*. The patient appeared somewhat round shouldered, and her head drooped well forward. Her gait was characterized by a slight lurching tendency and dragging of the left foot. General physical examination revealed no other abnormalities of note.

Neurologic Examination.—1. Strength of the muscles of the shoulder girdle and the biceps and triceps was approximately 20 per cent below normal; the pronators and supinators were severely affected, and alternating movements involving these muscles could not be performed; the extensor and flexor muscles of the forearms were very weak, being at least 40 per cent below normal on the right and 50 or 60 per cent below normal on the left; the intrinsic muscles of the hand were even more severely involved; the extensor muscles of the left great toe and foot showed slight weakness (10 to 20 per cent). 2. Fasciculation was noted at various times in the muscles of the shoulder girdle and the arm and thigh and was invariably detectable (usually to a conspicuous degree) in the forearms. 3. All deep reflexes were hyperactive, but those on the left, except at the ankle, were more active than the corresponding reflexes on the right; Hoffmann's sign was present bilaterally, and a Babinski reflex was obtained on the left side. 4. Slight spasticity of the muscles of both arms and of the left leg was present.

Laboratory Data.—Lumbar puncture showed clear fluid, under an initial pressure of 210 mm. of water, a negative reaction for globulin, a normal colloidal gold curve and negative reactions to the Wassermann and Kolmer tests. Other laboratory examinations, including complete blood studies and urinalysis, gave normal results. A roentgenogram of the sinuses showed nothing unusual except for "minimal thickening of the mucous membranes" of the left ethmoid cells on the left side. Roentgenograms of the cervical portion of the spine were normal.

Myographic Study.—Activity of the left deltoid muscle, the flexors of the left forearm and the extensors of the right forearm was associated with potentials of nearly twice the magnitude of those from the corresponding muscles of the opposite side in performance of the same work. In each instance the activity of the weaker muscles was associated with much greater variations of potentials, and rhythmic bursts of higher potentials occurred at the rate of approximately 3 to 4 per second. The potentials of the left abductor brevis were very low and abnormal, whereas the corresponding muscle on the right side produced regular potentials of greater magnitude.

Diagnosis.—The diagnosis was amyotrophic lateral sclerosis.

Treatment.—Trypan red therapy was decided on, and she was given a total of 160 cc. of a 1 per cent solution, in sixteen intravenous injections of 10 cc. each over a period of thirty-four days. This resulted in intense staining of the skin. The patient reported that she felt better after each injection, and the cramping pains of the left arm and the aching of the neck and shoulder were greatly improved. Fasciculation was considerably lessened in all muscles, progressively so toward the end of the course of injections and over the subsequent few weeks.

Follow-Up Study.—On Jan. 29, 1943, ten weeks after treatment was begun, fasciculations were reported as rare, except at the time of the menses. Lisping speech and uncontrolled laughter were present, as before. Burning of the eyes, photophobia and blurring of vision had been noted in the past month. The ocular symptoms were benefited by wearing dark glasses. In this connection, she reported that she had suffered from burning and smarting of her eyes for four or five years, that her eyes were sensitive to red and that she had worn dark glasses with benefit for several years. Examination showed slight fasciculation in her forearms alone (observed at the time of the menses), hyperactive but equal reflexes and an equivocal Babinski sign on the left side. She was given vitamin A, 25,000 units per day, for her eyes.

On Feb. 17, 1943 she was doing well. She could do things, such as manage a zipper, which she could not do before. Fasciculation was not noted in the legs and was only slight in the arms. The eyes were improved. Examination showed her speech and strength to be unchanged. Slight fascicular jerks were present in the muscles of the shoulders and arms, being more pronounced on the left. All deep reflexes were still very hyperactive, but about equal on the two sides. Ankle clonus was not observed. There was an equivocal Babinski sign on the left side.

Follow-Up Injections.—Trypan red was administered as follows: 50 cc. of 1 per cent solution in five injections, from Feb. 17 to March 29, 1943; 170 cc. of 1 per cent vital red in nine injections, from April 21 to July 13, 1943, and 60 cc. of 1 per cent trypan red in six injections, from July 20 to Aug. 13, 1943. Further injections of 10 cc. of a 1 per cent solution of trypan red were continued at three week intervals.

Examination on Oct. 18, 1943 showed that speech, posture and gait were somewhat worse. Slight fasciculation of the left lower eyelid and the left side of the face was noted. There was intermittent fasciculation of the biceps and triceps and the muscles of the forearms, being slight on the right and moderate on the left. Strength of the leg muscles was good. No wasting or fasciculation was noted in the legs. The deep reflexes were hyperactive but equal. Unsustained ankle clonus and a Babinski sign were elicited bilaterally.

In January and February 1944, she had bronchopneumonia in the left lung. When she was seen on March 6, fasciculations were less than on the previous examination. She believed that her speech had improved. Her condition otherwise was about the same. Injections of trypan red were continued at intervals of three weeks.

Myographic and Follow-Up Studies.—March 15, 1944: The potentials were smaller than in the previous myograms, especially those from the extensors of the left forearm, the left deltoid and the right adductor pollicis brevis. Tracings from the flexor muscles were about the same as before, except that their action was more evenly sustained. Except for a few gross twitches of the deltoid, no fascicular phenomenon was observed at this time.

August 14: Fascicular twitching in the muscles of the shoulder girdle and arms was present, as well as some in the thigh muscles. Her posture was

worse. Her gait was spastic, with short steps, and she had to be steadied. Speech was the same, or slightly worse. There was early atrophy of the tongue. Wasting of the deltoids and the muscles of the back was more marked than before. Reflexes and other signs were essentially unchanged.

She continued to insist that her condition was materially improved after each injection. Specifically, she stated that the fasciculations were less pronounced, her strength, speech and balance were benefited and her ability to work about the house was improved. The improvement was said to continue for approximately three weeks with an injection of 10 cc. of 1 per cent trypan red, and correspondingly for briefer periods after smaller injections. Her husband and mother repeatedly corroborated this statement.

August 29: She was hospitalized, after one month without treatment, with the hope of evaluating these points objectively. Two days after an injection of 10 cc. of 1 per cent trypan red, she said she felt stronger and steadier. The fasciculations were noted to be less; her speech was more intelligible, and her gait possibly was somewhat improved.

March 15, 1945: Her condition was essentially the same as on her last examination, except that her speech was less intelligible and fasciculations, wasting and weakness were slightly worse. She still felt improved after each injection, the medications being continued at intervals of three weeks.

Aug. 24, 1946: Slow progression of weakness and wasting was noted, and there was increased fasciculation of the pectoral muscles and the muscles of the back and neck. She had to be supported in walking. Her speech was unintelligible. Swallowing was difficult. Her weight was 46.4 Kg. Injections were discontinued.

Dec. 24, 1946: Her condition was essentially the same.

April 21, 1947: Her condition was reported as considerably worse.

Summary and Comment.—A housewife aged 35 experienced progressive wasting, weakness and twitching of the muscles, which led to treatment within one and one-half years of the onset of her illness. Examination revealed neurologic findings typical of amyotrophic lateral sclerosis. Her condition was judged to be moderately advanced, and the rate of progress of her disease at the time of the initial study was considered to be moderately rapid. Dye therapy was instituted and was maintained with follow-up injections every third or fourth week over a period of four years. Some evidences of improvement were observed, such as lessening of the muscle cramps and fasciculations, an increase in her strength and ability to accomplish specific tasks and suggestive improvement in her gait and speech. Although these beneficial effects were repeatedly observed, the benefit was transient and of relative significance only as compared with her condition and the rate of progress of her disease when the dye therapy was discontinued or when the follow-up injections were delayed. Although the disease process definitely appeared to be slowed, it was at no time entirely arrested, and she gradually lost in weight and strength as the wasting of her muscles progressed. Whereas the degree of involvement and rate of progression were judged to be moderate one and one-half years after the onset of her illness, the rate of progression was slow in the subsequent four years and nine months and repeatedly appeared to be modified by the dye therapy.

CASE 11 (classification 3).—G. W., a stock clerk and truck driver aged 34, noted weakness of his left ankle and left little finger two and one-half years prior to admission to the hospital. The entire left hand became weak two years before entry, and subsequently progressive weakness, wasting and fasciculation were observed in the muscles of both legs and arms. He was forced to discontinue work one and one-half years before admission. Parenteral injections of vitamin B complex and iron had been given from one to three times a week for two years. Vitamin E in large doses had been taken over the past one and one-half years.

His past and family histories were noncontributory.

Routine laboratory studies, including blood counts, serologic tests and urinalysis, revealed nothing abnormal. Roentgenograms of the spine were normal.

Examination showed a thin man of middle-aged appearance, who limped, with a left foot drop, and who moved his hands in flail-like fashion. General physical and neurologic examinations revealed nothing remarkable except for the motor and reflex changes. Fascicular twitchings of the perioral, the left periorbital, the deltoid and the pectoral muscles, and the muscles of the arms, forearms, hands and right calf were observed. Similar twitching was suggestively present in the tongue. Muscular atrophy involved all muscles of all the limbs, but was particularly noticeable in the left deltoid, the right biceps and triceps, the intrinsic muscles of the left hand, the right quadriceps femoris and gastrocnemius and the left tibialis and peroneal muscles. Weakness corresponded closely with the wasting. The patient had no grip in the left hand, could not flex the right forearm or extend the left forearm or wrist against gravity, and could not dorsiflex the left foot. Examination of reflexes showed hyperactivity of the biceps and knee jerks on the left side and slight hyperactivity of the radial reflexes. The right knee jerk and triceps reflex were hypoactive, and all the others were absent. No reaction was obtained to the Babinski test. His weight was 86.3 Kg.

Diagnosis.—The diagnosis was amyotrophic lateral sclerosis.

Treatment.—Ninety-four cubic centimeters of a 1 per cent solution of vital red was given in five injections over a period of six days; 173 cc. of a 1 per cent solution of trypan red was administered in fifteen injections over a subsequent period of twenty-four days. This treatment resulted in a brilliant reddish discoloration of the skin. No toxic effects were noted.

Follow-Up Study.—Aug. 24, 1944: On this day, when the final injection was given, the patient reported that the cramps in his thigh and calf muscles were greatly improved. He could balance better, and could climb stairs and roll from side to side in bed, activities which he previously could not perform. Muscular fasciculations were thought to be somewhat improved. Examination showed fasciculations only in the right triceps and the left adductor pollicis. Reflexes were essentially the same as before treatment, except for the right biceps and the right knee jerk, which were now within normal limits.

Sept. 4, 1944: The patient could use the right hand almost normally, although it was still very weak. Use of the left hand also was improving. He could extend the wrists. His balance and gait were improved. He had written a letter for the first time in six months. His weight was 89.1 Kg.

Oct. 2, 1944: Balance, posture and gait were improved. He could stand alone on his left toes. Slight fascicular twitchings were still observed at times in the triceps, pectoral and thigh muscles. All involved muscles of the limbs were considerably stronger and less flabby. Color was almost normal except about the eyes.

Dec. 2, 1944: Continued but less rapid improvement was observed. He had noted some increase in fascicular twitching during the night. He returned to work.

Jan. 15, 1945: Twitching and cramps in the feet were worse. Injections of 10 cc. of trypan red at monthly intervals were started.

March 19, 1945: He reported that twitching had diminished after the injection in January, and general improvement slowly continued. Ankle jerks were elicited but were hypoactive. His strength was greatly improved, especially in the legs. He could dance and run. His weight was 90 Kg.

Aug. 6, 1945: Twitching was worse, and weakness was more pronounced in the hands and arms, but not in the legs. These changes were observed to be gradual at first but later became more rapid. Injections of 5 cc. of trypan red every third week were started.

Sept. 26, 1945: The patient showed no improvement or increase in color of the skin. Weekly injections of 10 cc. of trypan red were started.

Nov. 6, 1945: He reported that improvement had started three weeks previously and that his condition was now the same as before the slump in August. Injections of trypan red were continued, 10 cc. being given every third week.

April 16, 1946: Improvement was maintained. Reflexes were within normal limits. The weight was 80 Kg.

Oct. 22, 1946: Twitching and weakness in the arms and hands had again developed within the past six weeks. Injections of trypan red were increased in frequency, 10 cc. being given every week.

Dec. 5, 1946: He had received six injections in the previous six weeks. This resulted in a considerable heightening of the color of his skin. Fasciculations were decreased and strength was noticeably improved in the hands and arms. His condition was now almost the same as before the relapse in October. Injections of 10 cc. of trypan red were continued every second week.

April 11, 1947: His general appearance and strength had slowly improved in the past five months. He had gained 6 pounds (2.7 Kg.) over the same period. He was able to lift objects with his left arm, which he could not do one year before. The strength in the right arm was good. The atrophy of the intrinsic muscles of his left hand appeared unchanged, but "his grasp was improved." The Babinski sign was reported as present and the right knee jerk as absent. Otherwise, the findings were essentially the same as before. The referring physician reported that "this man is showing definite and steady improvement and is able to work daily."

Summary and Comment.—A clerk and truck driver aged 34 had shown progressive wasting, weakness and fasciculations of muscles over a period of two years, a condition which had failed to respond to intensive vitamin therapy. Examination showed changes typical of amyotrophic lateral sclerosis. The degree of involvement was judged to be moderately advanced, while the rate of progression was only moderate. Dye therapy resulted in dramatic improvement and an apparent arrest of his disease process. Progression of the disease process recurred, however, on three subsequent occasions, once when the dye therapy was discontinued and again during periods of inadequate follow-up injections. In all instances, adequate dye therapy again appeared to arrest the disease and to improve his condition. Although unable to work for one and one-half years prior to the dye therapy, his condition improved sufficiently after the treatment that he was able to resume his work, which he has continued in the three subsequent years of observation and treatment.

COMMENT

The fact that well over one-half the patients in this study showed a diminution of fasciculation, while a definite modification of the disease process was observed in less than half the same patients, indicates a lack of correlation between fasciculation and the rate of progress of the disease process. The lack of correlation of fasciculation with respect to the progress of the disease was particularly noticeable in certain patients and in general was unmistakable in the first group. Although my enthusiasm was greatly bolstered in the early stages of this study by the concept that fasciculation might be used as an index of the degree of involvement or rate of progression of amyotrophic lateral sclerosis,[7] further observations did not substantiate this theory. My experience tends to corroborate the conclusions of Wechsler and associates,[8] namely, that there is no necessary correlation between fasciculation and the degree of involvement in amyotrophic lateral sclerosis.

The facts that the course of amyotrophic lateral sclerosis appeared to be modified in nearly one-half the patients and that an arrested state apparently could be achieved repeatedly in 2 patients suggest that this disease may have a toxic origin. This conclusion, of course, must be regarded as tentative, inasmuch as our group is not sufficiently large and our results are not sufficiently striking to warrant definite or final conclusions. Assuming, however, that the dye therapy is of value in some cases of amyotrophic lateral sclerosis, one is led to consider seriously the possibility of a toxic etiologic factor in this condition. The demonstrated protective effect of the dyes in experimental epilepsy and certain toxic conditions involving the central nervous system, and the predication of possible therapeutic value of the dyes in amyotrophic lateral sclerosis on this basis, would lend support to such a possibility.

That the results obtained were not more striking might be explained in two ways: 1. The effect of the dyes in lowering the permeability of the blood-brain barrier is rather limited and therefore could be expected to modify the course of the disease only in the less severe and acute cases. 2. Amyotrophic lateral sclerosis is not a single disease entity with but one origin, but, rather, is a disease complex with various possible etiologic mechanisms, any one of which may produce the clinicopathologic picture known by this name. The first possibility would appear to be consistent with the data on the rate of progress observed in individual patients and their relative response to the dye treatment, as

7. Swank, R. L., and Putnam, T. J.: Amyotrophic Lateral Sclerosis and Related Conditions, Arch. Neurol. & Psychiat. **49**:151-177 (Feb.) 1943.

8. Wechsler, I. S.; Sapirstein, M. R., and Stein, A.: Primary and Symptomatic Amyotrophic Lateral Sclerosis: A Clinical Study of Eighty-One Cases, Am. J. M. Sc. **208**:70-81 (July) 1944.

indicated in the table. Furthermore, in the experimental studies with vital red and trypan red, a decrease in the permeability of the blood-brain barrier of only about 30 per cent was effected after intense staining (more intense than in the studies on human subjects). A similar trial of an agent capable of modifying barrier permeability to a greater degree would be of great value in answering this question, and possibly at the same time in achieving a more definite and satisfactory therapeutic control of this disease.

The second possibility, that of a disease complex of multiple etiologic factors, has been discussed at length by Wechsler and his coworkers[8] and requires no further elaboration here. My data are not adequate to verify one or the other of these two possibilities. Even though the concept of multiple causation be correct, however, the first possibility might still operate to modify the effectiveness of the dye therapy, inasmuch as these two possibilities are not necessarily mutually exclusive.

Although the results of this study are by no means conclusive, they appear sufficiently encouraging to warrant further investigation and are reported in the hope that a better evaluation of the dye therapy may be achieved by more widespread trial.

CONCLUSIONS

The therapeutic trial of vital red and trypan red for amyotrophic lateral sclerosis is reported for 12 patients followed over a period of from two to seven years. The method of injection and the results are presented in detail. Fasciculations were diminished in the majority of patients; the rate of progress of the disease process was suggestively slowed in nearly half the patients, and an arrest apparently occurred in 2 patients. Although no final conclusions may be drawn from this limited study, the relation between treatment and improvement in several patients appeared more than coincidental, especially in those patients in whom a recurrence of the disease process, following discontinuance of the treatment, was again modified when adequate dye therapy was resumed. The possible significance of the results in establishing a toxic cause for amyotrophic lateral sclerosis is discussed. The study suggests that muscular fasciculation is not a reliable index of the progress of the disease. The results appear sufficiently encouraging to warrant further trial.

University of California Hospital (22)

News and Comment

APPOINTMENTS TO NATIONAL ADVISORY MENTAL HEALTH COUNCIL

The appointment of Dr. Leo H. Bartemeier, associate professor of psychiatry, Wayne University College of Medicine, Detroit, and Dr. Carlyle Jacobsen, dean of the graduate school, State University of Iowa, Iowa City, to the National Advisory Mental Health Council was announced today by Mr. Oscar R. Ewing, Federal Security Administrator. Dr. Bartemeier and Dr. Jacobsen succeed Dr. David Levy, assistant professor of psychiatry, Columbia University College of Physicians and Surgeons, New York, and Dr. Edward A. Strecker, professor of psychiatry, University of Pennsylvania School of Medicine, Philadelphia, whose terms on the Council expired on June 30, 1948.

Dr. David Levy has been appointed to serve on the research study section, an advisory body of the Council, and Dr. Grover F. Powers, professor of pediatrics, Yale University, New Haven, Conn., has also been appointed to the research study section, replacing Dr. Charles A. Janeway, professor of pediatrics, Harvard Medical School, Boston, on the latter's resignation from the research study section.

The National Advisory Mental Health Council is a body of six leading medical or scientific authorities outstanding in the study, diagnosis or treatment of psychiatric disorders which advises, consults with and makes recommendations to the Surgeon General on matters relating to the activities of the Public Health Service in the field of mental health. The other members of the Council are: Dr. Karl M. Bowman, professor of psychiatry, University of California Medical School, San Francisco; Dr. Alan Gregg, director, the medical sciences, the Rockefeller Foundation, New York; Dr. William C. Menninger, medical director, the Menninger Clinic, Topeka, Kan., and Dr. John Romano, professor of psychiatry, University of Rochester School of Medicine, Rochester, N. Y.

MEDICAL JOURNALS NEEDED ABROAD

Requests from libraries, medical societies and individual physicians in various devastated countries are being received almost daily. If physicians have extra copies of medical journals or copies for which they have no further use, it will be greatly appreciated if they will send them to the headquarters of the Association for distribution abroad.

CHILD GUIDANCE CLINIC IN THE ORANGES AND MAPLEWOOD, N. J.

A child guidance clinic under community sponsorship is to be established this fall in the Oranges and Maplewood in New Jersey. It will supplement the work of the Essex County Child Guidance Clinic, whose distinguished director was the late Dr. James S. Plant. The new clinic will emphasize treatment and will include on its staff a child psychiatrist, a clinical psychologist and psychiatric social workers. The clinic will be conducted in close cooperation with the public schools and the social agencies of the community; and an educational and preventive program through conferences and lectures to parents and teachers is also included in its plans.

Funds sufficient to insure employment of able and experienced professional leadership for the clinic have been made possible through joint action of the municipal governments of East Orange, Orange, West Orange, South Orange and Maplewood and by subscription of funds from a private endowment fund for child welfare. Events which led up to the founding of this clinic were popularly described in an article in the *Saturday Evening Post* (Aug. 7, 1948), entitled "The Case that Rocked New Jersey." The clinic is independently incorporated and will be administered by an autonomous board.

As this item goes to press, neither the psychiatrist nor clinical psychologist has been appointed. Further information concerning the clinic can be obtained from the coordinating and planning agency in the community which has sponsored the clinic, the Social Welfare Council of the Oranges and Maplewood, 439 Main Street, Orange, N. J.

OPENING IN CHILD PSYCHIATRY WITH SOCIAL WELFARE COUNCIL OF THE ORANGES AND MAPLEWOOD, ORANGE, N. J.

A position in child psychiatry is offered with the Social Welfare Council of the Oranges and Maplewood, Orange, N. J., the psychiatrist to serve also as medical director of the new Child Guidance Clinic of the Council, to be established this fall. A clinical psychologist and two psychiatric social workers are also to be appointed to the clinic staff.

Communications may be addressed to Mr. Paul G. Cressey, director, 439 Main Street, Orange, N. J.

RESIDENCY TRAINING PROGRAM IN NEUROPSYCHIATRY, VETERANS ADMINISTRATION

A limited number of openings are available at this time for appointment to the residency training program in neuropsychiatry of the Veterans Administration Department of Medicine and Surgery. This program is under the jurisdiction of the deans of the Boston medical schools (Harvard, Tufts and Boston University). Training in this program, which may be from one to three years, is given at the following institutions:

Cushing Veterans Administration Hospital.....Framingham, Mass.
Bedford Veterans Administration Hospital.....Bedford, Mass.
The Mental Hygiene Clinic of the Boston Regional Office, Veterans Administration.....Boston
West Roxbury Veterans Administration Hospital.....West Roxbury, Mass.
White River Junction Veterans Administration Hospital.....White River Junction, Vt.

Emphasis in the entire program is on psychiatry, with dynamic orientation, and includes closed ward, open ward and outpatient psychiatry, child psychiatry and neurology.

For information, write to the Chief Neuropsychiatrist, Veterans Administration Branch Office No. 1, 55 Tremont Street, Boston 8.

RESIDENCY PROGRAM IN NEUROLOGY, VETERANS ADMINISTRATION HOSPITAL

It is desired to announce that a residency program in neurology has been established at the Veterans Administration Hospital, New York. This has been approved by the American Board of Psychiatry and Neurology for a period of three years. Appointments are made for one to three years, beginning January and July.

Application forms may be obtained by writing to Earl Gluckman, M.D., Liaison Officer, Deans Committee, Veterans Administration Hospital, 130 West Kingsbridge Road, New York 63.

RESIDENCIES IN PSYCHIATRY, VETERANS ADMINISTRATION

Residencies in psychiatry are now available at the Veterans Administration Hospital, Gulfport, Miss. Training will be given at the hospital and in New Orleans under the supervision of Tulane University and Louisiana State University Schools of Medicine. The program, approved by the American Medical Association and the American Board of Psychiatry and Neurology, will include didactic and clinical instruction in all phases of psychiatry and basic neurology, with experience in the technics of treating neuropsychiatric adults and children. Applications should be addressed to Dr. H. W. Kostmayer, chairman of the Combined Deans' Committee, Tulane University of Louisiana School of Medicine, New Orleans.

SOUTHERN SOCIETY OF ELECTROENCEPHALOGRAPHY

The Southern Society of Electroencephalography was organized by the executive council of that society in Atlantic City, N. J., June 11, 1948. The first general meeting will be held at the time and place of the next meeting of the Southern Psychiatric Association. All persons in the southern area interested in becoming members of this organization are requested to communicate with the acting secretary-treasurer of the society, Dr. Samuel C. Little, 2111 Highland Avenue, Birmingham 5, Ala.

RESIGNATION OF DR. NATHAN BLACKMAN AS CHIEF PSYCHIATRIST, MENTAL HYGIENE CLINIC

Dr. Nathan Blackman has announced his resignation as chief psychiatrist, Mental Hygiene Clinic, Veterans Administration Facility, St. Louis. In association with Dr. Louis L. Tureen, he will open a neuropsychiatric clinic at 440 North Taylor Avenue, St. Louis.

Correction

An abstract of a paper by Dr. James G. Golseth and Dr. James A. Fizzell, entitled "Electromyographic Studies on Cats After Section and Suture of the Sciatic Nerve," which was read before the Chicago Neurological Society, was inadvertently appended to the end of the report of the Oct. 25, 1946 meeting of the Philadelphia Neurological Society in the March 1948 issue of the ARCHIVES.

Obituaries

CHARLES A. ELSBERG, M.D.
1871-1948

Charles Albert Elsberg was born in New York city on Aug. 24, 1871, the son of Albert and Rebecca Elsberg. He had three brothers and a sister. He was graduated from the College of the City of New York in 1890, the college which so signally honored him in 1935 with the Townsend Harris Medal, and again in 1947 with an honorary degree. In 1893 he was graduated from Columbia University College of Physicians and Surgeons, winning the Harsen Clinical Medal.

His professional life lends itself to a natural division into three periods. The first, from 1893 to 1909, may be termed "early Mount Sinai days." During this time he served his internship at the Mount Sinai Hospital, went abroad to study under von Mikulicz, on his return became assistant pathologist, then served his apprenticeship in surgery in the outpatient department and his early days on the general surgical service as adjunct surgeon. Toward the close of this period his interest in neurologic surgery was becoming manifest.

The second period covers the years from 1909 to 1929. It begins with the founding of the Neurological Institute and ends with his separation from the Mount Sinai Hospital. It could well be termed the years of dual interest. It was during this period that he was made associate surgeon (1911) and attending surgeon (1914) at Mount Sinai Hospital, while serving as attending surgeon to the Neurological Institute. While it marks the complete transition from general to neurologic surgery, it is also the time when he was at his best as a skilful general surgeon. During the period from 1924 through 1928 he was vice president of the New York Academy of Medicine.

The third period, from 1929 to 1937, the closing years of his professional activity, belongs to the Neurological Institute and the College of Physicians and Surgeons. It was in 1929 that the new Neurological Institute opened its doors and closer physical relationship was established with the medical school. He took an active part in planning the new building, especially the operating facilities. He often climbed in the unfinished structure to watch its progress.

The publications of Dr. Elsberg are made up of four books and five bound volumes of reprints. A glance at some of the titles in their chrono-

logic sequence will show into what period they fall. The first paper, concerned with the serum diagnosis of typhoid, was written while he was assistant pathologist at Mount Sinai Hospital. The date places it within a year of Widal's publications on that subject.

An early paper (1901), which dealt with the pathology, diagnosis and treatment of subphrenic abscess, was an important contribution at that time. He published several papers on perforations in typhoid. In 1909 he described an ingenious cannula for artery to vein transfusion as it was done in those days. His interest in thoracic physiology led to the development of a machine for intratrachal anesthesia.

His early experimental work dealt with thoracic physiology, the healing of heart wounds, the influence of posture on pneumothorax and intratracheal anesthesia. Later his investigations dealt with nerve regeneration and convulsions. Still later, the physiology of smell and vision engaged his attention.

The earliest publication on a neurosurgical subject was in 1904, a report of 2 cases of tumor of the cerebellopontile angle. There was then a lapse of five years before the next neurosurgical paper appeared.

In the second period the writings were almost exclusively on neurosurgical topics. As early as 1911 there was a report on 43 cases of laminectomy. It was during this period that the books "Diagnosis and Treatment of Surgical Diseases of the Spinal Cord and Its Membranes" (1916) and "Tumors of the Spinal Cord" (1925) were published. The other publications were in large part devoted to various aspects of lesions of the spinal cord, with some well chosen contributions to the surgery of cerebral tumors, such as acute tumors of the brain, and the relation of papilledema to these tumors.

Among the papers published during the early part of the third period were those on meningioma of the mesial part of the sphenoid ridge, technical aspects of operations for medulloblastomas and parasagittal meningiomas and the blood supply of gliomas. Later in the period, the greater part of his time and most of his writings were concerned with the basic investigations of the senses of smell and vision and with practical applications of these studies. He was not too busy to devote time to the *Bulletin of the Neurological Institute,* serving as its editor for several years. In addition, he carried on his teaching as professor of neurologic surgery at the College of Physicians and Surgeons.

In 1937 he retired from active hospital service and was made director emeritus at the Neurological Institute. The following year he served as president of the American Neurological Association and delivered the Charles K. Mills Lecture before that society. In 1941 he brought up to date his experiences in spinal cord surgery, in a book entitled "Surgical Diseases of the Spinal Cord." In 1944, under the title "The Story of a

Hospital," he related the history of the Neurological Institute of New York, in the organization and development of which he had played such an important part.

To have been an active general surgeon and then an equally busy neurologic surgeon, to have served in two hospitals as head of surgical services, to have engaged in teaching and research, to have published some one hundred and fifty medical articles and four books reveals one characteristic of Dr. Elsberg, his industry. It was practically a daily habit of his to leave his office in the very late afternoon with his brief case filled with unfinished work—work to be completed in part before retiring, in part before breakfast, after an early rising.

An accomplishment of his not so well known was his ability with pen and pencil. He could illustrate an operative procedure or could, and did, correct illustrations made for him by artists.

Of him it may truly be said that he had but two real interests, his work and his family. His loyalty to these two was almost fierce in its intensity. Had it been necessary to make a choice between them, his family would always have been first.

Outside his family, Dr. Elsberg had few intimates. While he was easy to approach, it was on a plane removed from the personal. He was at all times a gentleman—"a gentleman of the old school." He had considerable charm, and more than a touch of naivete.

His ability to think clearly, logically and intensely helped him in the solution of many medical problems. This ability, coupled with his attention to detail, made him the acknowledged leader in, and the outstanding contributor to, the development of spinal cord surgery.

In 1937 Dr. Elsberg married Jane Stewart. This gave him during his sunset years a beautiful companionship, which meant all the more to him because it came late in his life. Soon after marriage they moved to Stamford, Conn., where he began to lessen his activities. Nevertheless, it was during this time that the history of the Neurological Institute was published. He enjoyed his country life and the peace it brought; unfortunately, it was not to continue long enough.

In his last, long-drawn-out, illness, which ran the gamut from discomfort to severe pain, he never lost his fortitude. As a physician, he viewed himself objectively and drew on a reserve of strength and courage beyond belief. He died March 18, 1948.

Abstracts from Current Literature

Physiology and Biochemistry

ROLE OF WATER IN ETIOLOGY OF POLIOMYELITIS. R. R. SCOBEY, Arch. Pediat. **63**:567 (Nov.) 1946.

Scobey noted that the potential hydrocyanic acid content of plants that people commonly consume was increased during droughts when poliomyelitis is prevalent and that this poison is capable of producing symptoms and pathologic lesions such as those observed in this disease. While water is not technically classed as a food, it is an essential article of diet, which also contains a relatively high percentage of hydrocyanic acid under the same conditions. Rain water, which may be considered a pure water, soon becomes surface water, which quickly passes into the ground. The soil contains a high concentration of vegetable matter rich in cyanophore glucosides, which may be hydrolyzed in the soil to produce hydrocyanic acid or salts. A heavy rainfall during a long-continued dry spell may actually carry vegetable matter made more potent by drought to the ground water and to wells, springs and larger bodies of water, there to be concentrated by natural evaporation. Organic matter growing in and on the banks of rivers and their tributaries also increases that which was received from the soil, near and far, through the ground water. Garbage may increase the organic content in some of the streams of the country. Fish and other forms of animal life probably furnish enzymes to hydrolyze the hydrocyanic-acid-producing glucosides. The spread of poliomyelitis appears to follow water ways in many instances. It is suggested that the spring and fall overturns in bodies of water throughout the country would account, in part, for the appearance of poliomyelities in the spring, before vegetables and fruits have ripened adequately for human consumption, and the high incidence of the disease in the fall, when most of the harvest has been completed. It would also explain the sudden termination of epidemics of poliomyelitis with cold weather.

J. A. M. A.

CENTRIFUGAL DETERIORATION OF ASPHYXIATED PERIPHERAL NERVES. RICHARD A. GROAT and HAROLD KOENIG, J. Neurophysiol. **9**:275 (July) 1946.

Groat and Koenig studied the response of exposed nerves to electrical stimuli, noting muscular contraction or nerve action potentials. After control observations anoxia was induced by clamping the trachea. Thresholds were determined at various points along the nerve. After the induction of anoxia the most proximal point was always the first to show an increased threshold, and with the passage of time successively more distal points underwent a similar change. The nerve roots became inexcitable before the elevation of threshold at the midpoint of the nerve. In a partly deteriorated nerve, deterioration was more advanced in the central than in the peripheral half of a segment, and some fibers were blocked only in the peripheral half.

Groat and Koenig suggest that a given block along a given fiber involved but a short segment of the fiber, and blocking along a greater length resulted from

fusion of the short blocked segments. This proximodistal gradient of deterioration must be a manifestation of a gradient along the intact nerve.

FORSTER, Philadelphia.

THE HYPOTHALAMIC REGULATION OF SLEEP IN RATS. W. J. H. NAUTA, J. Neurophysiol. **9**:285 (July) 1946.

Nauta found that in the rat complete bilateral transection of the hypothalamus, regardless of the location of the section, interferes with the normal regulation of sleep. The location of lesions which produced disturbances of waking indicated the existence of a structure in the caudal portion of the hypothalamus and in the adjacent tegmentum of the midbrain which was of specific importance for the maintenance of the waking state in the absence of external stimuli. There was also an indication that a structure in the preoptic region was essential for the capacity of sleeping. Sleep is produced by the inhibitory action of the sleep center on the waking center. The lateral hypothalamic area seems more important for sleep and waking than the medial area, and since the medial bundle of the forebrain occupies this area, this structure may transmit impulses determining the sleep-waking rhythm. The hypothalamic centers involved in the regulation of sleep are topographically identical with those determining autonomic balance.

FORSTER, Philadelphia.

MECHANISM OF PUPILLARY DILATATION BY CORTICAL STIMULATION. ARTHUR A. WARD JR. and H. LESTER REED, J. Neurophysiol. **9**:329 (July) 1946.

Ward and Reed studied the pupillary dilatation produced in monkeys by electrical stimulation of area 8 of the cerebral cortex. They found the pupillary change to be a localized sympathetic response having all the properties of reciprocal innervation. Section of the cervical portion of the sympathetic chain abolished the change. The active dilator component travels over pathways involving the hypothalamus, and this corticohypothalamic pathway is not a direct one. The reciprocal inhibitory pathway from area 8 to the oculomotor nucleus is a direct projection.

FORSTER, Philadelphia.

PRESENCE AND ACTION OF ACETYLCHOLINE IN EXPERIMENTAL BRAIN TRAUMA. MURRAY B. BORNSTEIN, J. Neurophysiol. **9**:349 (Sept.) 1946.

Bornstein showed that as a result of experimental trauma acetylcholine is consistently presented in the spinal fluid in estimable quantities. This increase occurs within a few hours and persists up to forty-eight hours. This abnormal presence of acetylcholine is thought to be due to an excess production or release of the substance, insufficient destruction and consequent persistence within the intercellular spaces. Concussion produced changes in the behavior and in the electroencephalograms of the animals. Administration of atropine sulfate abolished the electroencephalographic changes and the stuporous condition. Perfusion of acetylcholine in physiologic concentrations produced high amplitude waves in the electroencephalogram, whereas perfusion in high concentrations produced flattening. Intracisternal injection of acetylcholine with physiologic or higher concentrations produced alterations similar to those produced by perfusion. Atropinization of the animals also prevented the changes produced by intracisternal injection of acetylcholine. Bornstein concludes that the free acetylcholine may be one of

the physiologic factors underlying the acute paralytic and excitatory phenomena of cerebral concussion.

FORSTER, Philadelphia.

RESPONSES OF SINGLE HUMAN MOTOR UNITS TO ELECTRICAL STIMULATION. E. KUGELBERG and C. R. SKOGLUND, J. Neurophysiol. **9**:391 (Sept.) 1946.

Kugelberg and Skoglund studied the responses to electrical stimulation of single motor units in the human subject. Specially devised stimulators were employed, and the cathode was placed over a peripheral nerve. Exponential or linear rising currents were employed. Study of the accommodation curves reveals that the single muscle twitch is accompanied with discharges from several motor units. The technic also permits study of the frequency and duration of single unit discharges to continuous stimuli. The adaptation time—the length of time until the motor unit ceases to discharge—is similar in animals and man and is related to the accommodation. There are significant differences in excitability between the proximal and the distal portion of a peripheral nerve, and these differences may be due to the diminution in diameter of a fiber after branching.

FORSTER, Philadelphia.

PAIN ON STIMULATING THE DISTAL SEGMENTS OF DIVIDED PERIPHERAL NERVES. J. LAWRENCE POOL and JOHN A. BRABSON, J. Neurosurg. **3**:468 (Nov.) 1946.

Pool and Brabson report 4 cases of severance of peripheral nerves in which stimulation of the distal segment produced pain felt in regions supplied by intact adjacent nerves.

Two cases of median nerve injury are reported: In one the injury was in the lower third of the arm, and in the other, in the lower third of the forearm. Both motor and sensory functions supplied by the median nerve were destroyed distal to the injury. On stimulation of the distal segments, pain was felt in an area supplied by either the ulnar or the radial nerve. Blocking of one of these nerves by local infiltration with procaine hydrochloride abolished the pain or referred it to an adjacent normally functioning unblocked nerve.

Two injuries of the ulnar nerve with severance of the nerve in the middle and distal thirds of the forearm are described. In these instances, stimulation of the distal segments gave rise to pain in an area supplied by the median nerve. Local block of the median nerve with stimulation of the distal ulnar segment now elicited pain from an area supplied by the radial nerve.

In all cases, care was taken that (1) no spread of electrical current occurred, (2) there was no motor response after stimulation and (3) the area supplied by the severed nerve was completely insensitive to cutaneous stimulation.

The authors conclude that the sensory response from stimulation of an isolated nerve segment reached an intact nerve by (1) passing over direct anastomosing branches, (2) inducing changes in the chemical mediator of sensory units at the zone of overlap of adjacent nerves or (3) evoking a local sympathetic reflex relayed centrally by an intact nerve.

The study is of practical significance in that pain on stimulation of peripheral nerves, distal to a neuroma, is not an absolute index of functional continuity of the nerve.

TOZER, Philadelphia.

THE EFFECTS OF SUBARACHNOID INSTALLATIONS OF THERAPEUTIC CONCENTRATIONS OF PENICILLIN SOLUTION ON THE CENTRAL NERVOUS SYSTEM. ALEX GERBER, EDWIN BOLDREY, H. J. MCCORKLE and HELEN WARMER, J. Neurosurg. **3**:533 (Nov.) 1946.

Penicillin was injected into the cisterna magna and ventricles of dogs in a series of experiments by Gerber and associates. The solution used was 1,000 units per cubic centimeter, and 1 to 2 cc. was injected. There resulted temporary pleocytosis and increase in cerebrospinal fluid protein, but no abnormal neurologic signs appeared. Autopsy revealed no significant pathologic changes.

Penicillin injected into the lumbar region caused a notable increase in viscosity of the spinal fluid. The authors conclude that this change was due to the increase in protein and the slow diffusion of penicillin and spinal fluid from the lower lumbar region to the higher cisternal region.

TOZER, Philadelphia.

EFFECT OF CEREBRO-SPINAL FLUID ON INTERACTION BETWEEN RH AGGLUTININS AND AGGLUTINOGENS. RACHEL JACOBOWICZ and LUCY M. BRYCE, M. J. Australia **2**:740 (Nov. 23) 1946.

Jakobowicz and Bryce point out that specimens of human serum containing strong anti-Rh agglutinins did not agglutinate group O Rh_1 cells when chemically normal cerebrospinal fluid was used (instead of saline solution) as the diluent for the serum dilutions and the red cell suspensions. The inhibition occurred irrespective of whether the cerebrospinal fluid was obtained from Rh-positive or Rh-negative persons. The inhibition of Rh agglutination by cerebrospinal fluid can be overcome by the addition of human serum or human albumin. Artifically prepared fluids containing the main known chemical components of cerebrospinal fluid do not mask Rh agglutination, nor does the chemically similar allantoic fluid of the chick embryo; but cerebrospinal fluid from 1 rhesus monkey and 1 rabbit had a similar effect on human Rh agglutination as did 15 samples of human cerebrospinal fluid. The inhibiting effect of the cerebrospinal fluid may be related to the blocking phenomenon.

J. A. M. A.

Neuropathology

ETIOLOGIC FACTORS IN THROMBOENDARTERITIS OBLITECANS, VON WINIWARTER-BUERGER TYPE, IN GRANULAR ATROPHY OF THE CORTEX. FERDINAND MOREL, Schweiz. Arch. f. Neurol. u. Psychiat. **57**:350, 1946.

Morel expresses the view that the term granular atrophy of the cerebral cortex should be restricted to the symmetric, or systematized, type of this condition, in which a band of atrophy of uniform width is distributed in each hemisphere along a line corresponding to the boundaries of the three great vascular territories. Zones of granular atrophy in cases of the nonsystematized type generally surround foci of gross softening. When the second variety of granular atrophy is due to thromboendarteritis obliterans, clinical evidence of the underlying vascular disease may be observed in the retina, as well as in the extremities, and signs of focal cerebral involvement are common. The author's experience would indicate that clinical evidence of this sort is generally lacking in cases of the systematized type of granular atrophy.

The author reports the results of clinical and postmortem study in 7 cases of the symmetric type of granular atrophy of the cerebral cortex. Although in the area of granular atrophy the cortical arteries were frequently devoid of blood and hyalinization of the arterial walls was common, in no case were intimal changes characteristic of thromboendarteritis obliterans encountered. Except for 1 patient, a man aged 54 with aortic insufficiency, all patients were of advanced age; yet a notable degree of arteriosclerotic change was often lacking.

In conclusion, the author expresses the belief that the systematized type of granular atrophy of the cerebral cortex is due to a combination of local and general factors. Changes in the terminal branches of the cerebral arteries which develop with advancing age, would, according to his point of view, render the corresponding portions of the cortex peculiarly vulnerable to transient circulatory disturbances of a general character.

DANIELS, Denver.

LESIONS OF CENTRAL NERVOUS SYSTEM PRODUCED BY CARBON MONOXIDE POISONING. J. LHERMITTE and DE AJURIAGUERRA, Semaine d. hop. de Paris **22**:1945 (Nov. 14) 1946.

According to Lhermitte and Ajuriaguerra, the changes in the brain in carbon monoxide poisoning differ widely, depending on the time elapsed between the exposure and necropsy. Hemorrhages, necrobiosis, necrosis and edema characterize the anatomic picture in cases in which death occurred rapidly. The changes may involve primarily the lenticular nuclei but affect also the subcortical white matter, the hippocampus, the substantia nigra and the cerebellum. Changes in the vascular network with infiltration of the walls by neutral lipids and by a peculiar substance containing ferric salts, calcium and lipids may be observed in cases in which the poisoning continues for a prolonged period or in which death is delayed. A diffuse demyelination of the entire white matter of the brain, similar to Schilder's diffuse cerebral sclerosis, may be observed in cases in which death occurs after a long period of remission. It is suggested that in carbon monoxide poisoning a toxic factor in addition to the anoxic factor, affects the neuroglia and the vascular network, with specific involvement of the basilar region and the white fibers of the centrum ovale.

J. A. M. A.

Psychiatry and Psychopathology

RELATION OF PERSONALITY DISTURBANCES TO DURATION OF CONVALESCENCE FROM ACUTE RESPIRATORY INFECTIONS. K. BRODMAN, B. MITTELMANN, D. WECHSLER, A. WEIDER and H. G. WOLFF, Psychosom. Med. **9**:37, 1947.

The authors undertook to ascertain the relation of personality disturbances and the duration of convalescence from acute infections of the respiratory tract. The Cornell Service Index was used as a measure of personality disturbance, and the duration of military hospitalization, as the measure of convalescence. The statistical studies were carried out on patients with nasopharyngitis, tonsillitis, bronchitis and pneumonia in three military hospitals.

In one hospital, 787 white patients with minor acute infections of the respiratory tract were studied. The average duration of hospitalization for 546 patients without significant personality disturbances was 4.8 days. For the 241 patients

with personality disturbances the average duration of hospitalization was 5.5 days, convalescence being prolonged by as much as 80 per cent, with an average of 15 per cent.

The average duration of convalescence was related to the attitude of the ward officer. One ward officer kept his white patients hospitalized 90 per cent longer than did any other ward officer in the hospital. Ward officers who were attentive to the complaints of patients kept patients with personality disturbances proportionately longer than patients without personality disturbances.

The authors also studied 292 Negro patients treated by the same ward officers in the same wards. Five of seven ward officers kept their Negro patients with personality disturbances for shorter periods than they did those without personality disturbances.

In the second hospital, 135 patients were examined. Convalescence was prolonged up to 109 per cent, with an average of 22 per cent for patients with personality disturbances. In the third hospital group, of 163 patients, convalescence was prolonged up to 48 per cent, with an average of 40 per cent for patients with personality disturbances.

The authors also infer that the portion of the population hospitalized for acute infections of the respiratory tract has a higher incidence of personality disturbances than the portion not so hospitalized.

FRANKEL, Philadelphia.

THE INCIDENCE OF PERSONALITY DISTURBANCES AND THEIR RELATION TO AGE, RANK, AND DURATION OF HOSPITALIZATION IN PATIENTS WITH MEDICAL AND SURGICAL DISORDERS IN A MILITARY HOSPITAL. K. BRODMAN, B. MITTELMANN, D. WECHSLER, A. WEIDER and H. G. WOLFF, Psychosom. Med. **9**:45, 1947.

The Cornell Service Index was used to investigate the number of symptoms to which patients in medical and surgical wards admit. The study is based on the data for 611 white and Negro enlisted men hospitalized for a wide variety of conditions. A score of 23 or more on the Cornell Service Index was taken as evidence of a high neurotic potential.

The study reveals that 29 per cent of white patients had high neurotic potentials, as compared with 22 per cent of troops on duty. For Negro troops the figures were 50 and 36 per cent, respectively. Of the hospital patients, the range was from 15 per cent for patients hospitalized for infections of the eye, ear, nose and throat, to 49 per cent, for those hospitalized for hemorrhoids.

Noncommissioned officer patients, both Negro and white, were less frequently neurotic than privates and privates first class. Of white privates and privates first class, 33 per cent had scores over 23; and of the noncommissioned officers, 17 per cent had such scores. For Negro patients, these scores were 50 and 24 per cent, respectively.

White patients with significant neurotic scores were on the average of three years younger than those with scores less than 23. Of Negro patients, those with neuroses were, on the average, two years older.

In groups of patients hospitalized because of hemorrhoids, hernias, acute appendicitis and primary atypical pneumonia, it was found that the duration of hospitalization was 12 per cent longer for patients with personality disturbances. In the group with hemorrhoids, there was a larger number of personality disturbances than in the other groups.

FRANKEL, Philadelphia.

BODILY REACTIONS DURING ABREACTION. ROBERT L. MOODY, Lancet **2**:934 (Dec. 28) 1946.

Moody gives a brief explanation of the therapy of abreaction under narcosis, stating that it not only is a factual recall of the traumatic incident but is also accompanied with full expression of the emotions and at least partial repetition of the bodily movements associated with the original incident. He then gives a detailed report of a case in which a localized specific somatic reaction was shown during abreaction.

A man aged 35 was admitted to the hospital because of attacks of somnambulism accompanied with aggressive behavior. He had been hospitalized for this condition in 1935, and physical methods had been used to restrain him, his hands being tied behind his back during sleep on one occasion. This incident was abreacted under narcosis, and wheals appeared on both forearms; gradually these became indented and finally fresh petechial hemorrhages appeared along their course. Three other cases are cited briefly. In 1 there was recurrence of swelling of an ankle which had been injured in the original incident; in another, localized ischemia of the extremities in an abreaction of a prolonged immersion in cold water, and in a third petechial hemorrhages developed and bruising along the tenth rib, which had been fractured in the original incident.

MADOW, Philadelphia.

Meninges and Blood Vessels

MENINGOCOCCEMIA: A DESCRIPTION OF THE CLINICAL PICTURE AND A COMPARISON OF THE EFFICACY OF SULFADIAZINE AND PENICILLIN IN THE TREATMENT OF THIRTY CASES. J. MURRAY KINSMAN and C. ANTHONY D'ALONZO, Ann. Int. Med. **24**:606 (April) 1946.

During a period of thirty-one months in an Army camp, 33 proved cases of meningococcemia were observed and at least 29 cases in which the diagnosis was not confirmed bacteriologically but in which the clinical picture was so characteristic that they could be considered cases of meningococcemia. During the same period 111 cases of meningococcic meningitis were seen. In this series, for every 2 cases of meningitis there was approximately 1 case of meningococcemia without meningitis.

For the purpose of this study, the clinical material was confined to patients seen between February 1944 and June 1945. During this time 61 patients were admitted to this hospital with meningococcic infection, of whom 31 had meningitis, 15 had proved meningococcemia and 15 had unconfirmed meningococcemia. The latter group, of 30 cases of meningococcemia, confirmed and unconfirmed, constitutes the basis for this report. The range of ages was from 18 to 38 years, the average being 24. One patient was a Negro, the others were white persons. The average duration of military service was three months. Nine of the cases occurred in January, 4 in February, 3 in March, 3 in April, 2 in May, 4 in June, 3 in July, 1 in September and 1 in October.

It seems important to quote directly from this paper the authors' description of patients who had proved meningococcemia.

"There were prodromal symptoms in each instance: 11 patients had acute upper respiratory infections averaging one day in duration, and every patient had some fever, averaging one day in duration. In nearly every case, the acute illness was ushered in by chills, increase in fever, and headache. A rash developed

in every patient but one. Two-thirds of the patients had nausea and vomiting, and three-quarters of them had joint pains. The admission temperature ranged from 99 to 104° and the highest temperature from 102 to 105°. The headache was conspicuously different from the generalized "splitting" or "bursting" type so characteristic of meningitis: it was throbbing in nature and usually frontal in distribution.

"Although the characteristic eruption in meningococcic infections has generally been considered to be one of a hemorrhagic nature, yet in the cases of meningococcemia here reported, the typical lesion was a maculopapular one. Many of the macules took the form of pink plaques similar to the 'rose spots' of typhoid fever. These varied in size from 2 to 3 millimeters in diameter to areas of 10 to 12 square centimeters. In approximately half of the patients, hemorrhagic lesions were also present in the form of petechiae or purpuric spots; frequently these petechiae appeared in the center of the macules. Several patients exhibited all varieties of the rash concomitantly. Many of the lesions were tender to pressure, especially the hemorrhagic forms. In some cases only a few indistinct and isolated spots were present, whereas in others the rash was widespread and coalescent. The most common locations were the shoulders, axillae, arms, chest, legs, abdomen and back, in the order named; the face was not involved in any of the patients. Buccal mucous membrane and conjunctival petechiae were seen in several instances.

"The leukocyte count varied from 10,000 to 25,000, averaging 14,000, and the percentage of neutrophiles from 80 per cent to 96 per cent.

"The meningococcus which was recovered from the blood was of Group 1 in 14 cases and of Group 2A in one.

"The spinal fluid was examined in 10 patients, on six of whom three punctures were done for the purpose of assaying the fluid for penicillin. In every instance the cell count, smear and culture were normal or negative."

Kinsman, D'Alonzo and associates compared the clinical results in the 15 proved and the 15 unconfirmed cases. They showed that, except for the blood culture, the clinical pictures in the two groups were essentially identical. The average duration of symptoms prior to diagnosis was less than four days; every patient had fever and a rash with 1 exception; most of them had an infection of the upper respiratory tract, chills, headache and nausea; half of them had pains in the joints. The typical rash was maculopapular rather than hemorrhagic, as is generally described.

This series of 15 proved and 15 unconfirmed cases is compared with a series of 18 proved and 14 unconfirmed cases seen at the same hospital in a four month period in 1943, and reported by other authors. There were no essential differences between the proved cases or between the unconfirmed cases in the two series. Moreover, in both series no appreciable differences could be discovered between the proved and the unconfirmed cases. This lends further support to the conclusion that meningococcemia can, and should, be diagnosed clinically.

Spinal punctures were performed on 19 patients. In none did meningitis develop. The fact that treatment was already under way, or was instituted quickly could have prevented infection of the meninges. The authors conclude that spinal puncture in meningococcemia is a safe procedure.

Twelve of the patients were treated with sulfadiazine and 18 with penicillin. The therapeutic results were identical except that the temperature rached normal twelve hours earlier in the penicillin-treated than in the sulfadiazine-treated group.

GUTTMAN, Philadelphia.

Diseases of the Brain

CYSTIC CEREBELLAR ARACHNOIDITIS. RAYMOND K. THOMPSON, J. Neurosurg. 3:461 (Nov.) 1946.

Thompson states that cystic cerebellar arachnoiditis is an inflammatory reaction of the leptomeninges in the region of the cisterna magna. Scarring and thickening of the meninges results in partial obstruction of spinal fluid flow, and the cisterna magna becomes dilated, producing an arachnoid cyst.

The clinical picture is one of both internal hydrocephalus and local cerebellar pressure due to an expanding lesion, following craniocerebral trauma, in the posterior fossa. Herniation of this mass through the foramen magnum may give rise to symptoms of suboccipital neuralgia. Thompson reports a case in which the neuralgia was an important symptom, the pain being relieved by flexion of the head. It was surmised that flexing the head pulled the cyst and cerebellar tonsils from the foramen with abrupt subsidence of symptoms. A cerebellar cyst was observed at operation and was removed. The patient was asymptomatic in two weeks and was normal on follow-up examination after six months.

The case is of interest in that patients with suboccipital neuralgia following cranial trauma are not rare and are at times relieved by lumbar puncture. The cystic membrane is undoubtedly ruptured during withdrawal of fluid, with resumption of normal circulation.

TOZER, Philadelphia.

CEREBRAL GRANULOMA DUE TO SCHISTOSOMIASIS JAPONICA. HOMER S. SWANSON, J. Neurosurg. 3:538 (Nov.) 1946.

Swanson reports a case of intracranial granuloma in a patient aged 33, who had been discharged from the Army after serving in the South Pacific. Six weeks previous to admission to the hospital he had had a severe frontal headache, followed in two hours by blurred vision and a generalized convulsion. The headaches persisted, and five weeks later nausea and vomiting developed and he had one focal sensory seizure, limited to the left arm. He was slightly incoordinated, and his left arm was weak on admission to the hospital. He had spent approximately four years in the South Pacific, had experienced three attacks of dengue fever during this time and had recovered without complications or sequelae. He also had four attacks of an illness characterized by abrupt onset of scrotal and penile edema, associated with headache, malaise and fever. Each attack lasted about five days and then subsided, with no after effects. The stool and blood had been examined several times for the presence of schistosomes.

Examination revealed only early papilledema of the left eye and hyperreflexia of the left extremities, without pathologic reflexes. There was constant eosinophilia, but no parasites were found in either the blood or the stool. A ventriculogram revealed a lesion in the right occipital lobe. At operation, a tumor was located with difficulty, in the occipital lobe near the calcarine area. It was necessary to resect the occipital lobe as far forward as the posterior horn to remove all of the tumor. The patient responded satisfactorily, but residual left hemianopsia developed.

Microscopic sections showed an inflammatory process of the leptomeninges consisting of numerous granulomas, extending into the sulci and adjacent brain substance. Several large parasitic ova were seen in the granulomatous areas. No adult forms were seen. Occasional central necrosis with polymorphonuclear leukocytes were seen, but no areas of actual caseation were present. Numerous eosino-

phils and plasma cells with some lymphocytes were at the periphery of the granulomas. Perivascular infiltration of lymphocytes was present at some distance from the actual lesions, and the adjacent brain tissue showed edema and regeneration of the ganglion sells.

TOZER, Philadelphia.

A CASE OF CEREBRAL MALARIA IN GREAT BRITAIN. J. B. RYDER and R. T. TOWSON, Brit. M. J. **2**:815 (Nov. 30) 1946.

Ryder and Towson report the case of a steward aged 26 with cerebral malaria producing coma. The patient was at first treated for influenza, but when he suddenly became unconscious, on the fourth day of illness, he was sent to the hospital with a provisional diagnosis of malaria. Since he had recently returned from an endemic center of malignant tertian malaria, the diagnosis of cerebral malaria was considered and was later confirmed by laboratory studies. The patient recovered after treatment with large doses of quinine. The case is reported to emphasize the importance of considering cerebral malaria as a cause of coma and to stress the necessity for instituting treatment early.

ECHOLS, New Orleans.

CYSTICERCOSIS OF THE POSTERIOR FOSSA. GERMAN HUGO DICKMANN, Prensa méd. argent. **33**:1628 (Aug. 9) 1946.

Dickmann reports 4 cases of cysticercosis of the brain, 3 with lesions in the basilar cisterns and 1 with the parasite within the fourth ventricle. In each case a diagnosis of tumor of the posterior fossa was made prior to operation. Ten cases with involvement of the nervous system were collected from the literature; in 1 the lesion was in the spinal cord, and in the others the cysts were cerebral and meningeal in location. Cysticercosis is less frequent in Argentina than in Mexico and Chile. The clinical picture in all cases was that of increased intracranial pressure. In 1 of the 4 cases moria was present. In 3 cases there was bilateral papilledema, and in 1 bilateral primary optic atrophy; extraordinary dilatation of the ventricles was found after ventriculography in the case with primary optic atrophy. In all 4 cases the blood showed eosinophilia (count, 3 to 6 per cent). In 1 of 2 cases in which the spinal fluid was examined there was an increase in eosinophils; in 1 of these cases the Guillain reaction was like that described by Guillain and associates in cysticercosis (*Compt. rend. Soc. Biol.* **95**:455, 1926). The patient with cysticercosis of the fourth ventricle showed the Bruns syndrome, with headache, dizziness and vomiting in the standing position, which disappeared when lying down. One of the patients died after operation; the other 3 did well. The cysticercus of the fourth ventricles was removed through an incision in the vermis. The symptoms cleared up, and the patient was well thirty months after the operation.

N. SAVITSKY, New York.

LEFT HEMIATROPHY ASSOCIATED WITH PAINFUL NODULAR LIPOMATOSIS. C. F. CARREGA CASAFFOUSTH and DIEGO BRAGE, Prensa méd. argent. **33**:1643 (Aug. 9) 1946.

An obese woman aged 49 gave a history of pain in the left arm and shoulder region twenty years previously, at which time she had intestinal amebiasis. Examination revealed painful fat pads in various parts of the body. The pain was definitely worse before her menstrual periods, which had continued to be regular.

Neurologic examination showed no evidence of focal disease of the nervous system. There was weakness of the left side of the body. Examination of the spinal fluid showed nothing significant. A roentgenogram of the skull showed a normal sella turcica. The Minor test showed some diminution of sweating on the left side; the reactions to all the other vegetative tests were negative. Oscillometric studies showed slight diminution of pulsation in the middle third of the left arm and the lower third of the left leg. The intradermal test with histamine showed no difference between the two sides of the body. Biopsy of the skin revealed nothing pathologic; biopsy of a subcutaneous nodule showed fatty tissue with some evidence of inflammatory reaction (lymphocytes, plasma cells and fibroblasts). Biopsy of one of the muscles on the left side showed definite muscular atrophy. An electroencephalographic study gave negative results, and the basal metabolic rate was normal. Some osteoarthritis of the lower cervical vertebrae appeared on roentgen examination. The specific dynamic reaction of protein was unaltered. There was 420 mg. of fatty acid per hundred cubic centimeters of blood (upper limits of normal); there was some increase of creatinine and cholesterol in the blood. Chronaxia showed changes of the neuritic type in the muscles of the left side of the body. The authors believe the hemiatrophy and lipomatosis were probably both due to a central disturbance of the autonomic nervous system.

N. SAVITSKY, New York.

Diseases of the Spinal Cord

PATHOLOGIC INTERVERTEBRAL DISK AND ITS CONSEQUENCES. OLAN R. HYNDMAN, Arch. Surg. **53**:247 (Sept.) 1946.

Chronic pain in the lower part of the back is commonly caused by degeneration of the intervertebral disk, a condition which leads to undue stresses and strains on the perispinal and lumbosacral ligaments. The clinical picture is that of aching in the lower part of the back, secondary muscle spasm and pain radiating to the hip and thigh. The last mentioned pain is referred in nature, as it can be abolished by paravertebral injection of procaine hydrochloride. The treatment of patients with simple degenerating disk consists in stabilization of the lower part of the back by bed rest and braces. In severe cases, relief is obtained by surgical measures (fusion.)

Herniation and rupture of the nucleus pulposus is only an advanced stage of the degeneration of the disk. If the degenerated and thinned annulus fibrosus is unable to retain the nucleus pulposus, herniation, and finally rupture, of the nucleus occur, even without trauma. Herniation of the disk is associated with signs of compression of the adjacent nerve root or roots, namely, radiating sciatic pain which is increased by cough and sneeze, paresthesias and loss of reflexes.

Hyndman expresses the opinion that degeneration of the disk is probably developmental in origin and that the role of trauma is only accessory, a view which may gain considerable medicolegal significance. He does not believe that trauma to the disk by lumbar puncture could conceivably be responsible for later rupture of the disk.

A degenerated disk shows a thinned annulus fibrosus and a nucleus pulposus of reddish color and mushy consistency. The normal mucoid structure of the nucleus is replaced by fibrocartilaginous metaplasia, but histologic signs of inflammation are absent.

A detailed classification is given of the various stages of the degenerating disk, from simple degeneration to complete rupture. A ruptured disk may be in-

completely sequestrated ("green disk") or totally sequestrated ("mature disk"). The sequestrated portion may be pocketed if the disk is only partially degenerated. The extruded nucleus pulposus may be located opposite the vertebral body, instead of being in contact with the disk from which it originated ("dissecting type"). A herniated disk does not calcify, but osteophytic spurs from the margins of the vertebra may surround it. When the herniation occurs into an intervertebral foramen, two nerve roots are simultaneously compressed, for example, the fourth and fifth nerve roots by a rupture of the fourth lumbar disk, and the fifth lumbar and first sacral nerve roots by a rupture of the lumbosacral disk. Because of the lateral and concealed position of such a herniation, the lesion may be easily missed in a myelogram, and even at operation, unless the intervertebral foramen is thoroughly unroofed.

Plain roentgenograms of the lumbar portion of the spine give little help for the diagnosis of a ruptured disk; reduced height of an intervertebral disk is not proof of the presence of a herniation. Myelography has only limited value and should be reserved for cases presenting special problems of differential diagnosis.

The author unreservedly recommends surgical removal if the clinical signs of herniated disk are typical. The degenerated portion of the disk should be removed as radically as possible to prevent recurrence. After operation, a firm union of the vertebral bodies is established, thus stabilizing the spine. The author believes that in only a few cases need there be primarily fusion by bone grafting. It is advisable to keep the patients in bed for three weeks after operation to obtain proper consolidation of the spine. Sometimes prolonged rest on hard mattresses, with the lumbar part of the spine in lordotic posture, may be required to overcome residual pain in the back and muscle spasm.

LIST, Grand Rapids, Mich.

SPREAD OF INFECTIVE HEPATITIS AND POLIOMYELITIS IN EGYPT. C. E. VAN ROOYEN and G. R. KIRK, Edinburgh M. J. **53**:529 (Oct.) 1946.

Van Rooyen and Kirk think that both infective hepatitis and poliomyelitis are primarily intestinal maladies. The carrier as well as the immunity rates at the time of an epidemic have never been accurately surveyed for lack of convenient methods. In susceptible persons who ingest infective hepatitis virus the secondary complication of jaundice develops more frequently than does secondary paralytic phenomena in those who ingest poliomyelitis virus. The authors interpret the epidemiologic behavior of infective hepatitis in the light of the discovery of the causal virus in human stools. Reference has been made to the spread of infection under conditions under which British troops served in the Middle East force.

J. A. M. A.

REFRACTORY SCIATICA DUE TO NEUROFIBROMATOSIS OF THE CAUDA EQUINA. JULIO DIEZ, Rev. Asoc. méd. argent. **60**:273 (May 15) 1946.

A man aged 62 had sciatic pain of five years' duration, the pain developing after a fall on his buttocks. He had severe pain in the lower part of the back for fifteen days, with radiation down the posterior aspect of the right lower limb. There was intensification of pain with active and passive movements, especially on extension of the right leg and foot. A year before admission a number of cutaneous tumors were removed; they proved to be neurinomas. He had difficulty in walking because of pain in the right sciatic nerve. On admission he had lumbar scoliosis, spasm of the right spinal lumbar muscles and limitation of motion of

the lumbar portion of the spine. Coughing and straining intensified the pain. There were a positive Laségue sign on the right side and atrophy of the right calf. The knee and ankle jerks were absent; there were no sensory changes. Roentgen examination showed osteoarthritis. Lumbar puncture revealed partial block, with no significant increase in protein. Injection of an opaque substance into the spinal canal showed interruption of the column, suggesting the existence of more than one tumor. Laminectory revealed the presence of three distinct tumors attached to the cauda equina; all were neurofibromas.

The diagnosis of probable neurofibromatosis of the cauda equina was made prior to operation. The presence of at least two tumors was suspected. The author notes the significance of the trauma which preceded the onset of the complaints. Tumors which hang from nerve roots can be displaced suddenlly by accidents. The case illustrates the value of contrast mediums in the diagnosis of sciatic syndromes. The author emphasizes the resemblance of this syndrome to that of a herniated disk.

N. SAVITSKY, New York.

Peripheral and Cranial Nerves

INVESTIGATION OF VESTIBULAR FUNCTION AFTER HEAD INJURY. D. G. PHILLIPS, J. Neurol., Neurosurg. & Psychiat. **8**:79 (Jan.-April) 1945.

Phillips investigated disturbances of vestibular function in 449 cases of head injury and reports in detail 57 cases, which he classified into two series. In the first series, comprising 50 cases, hearing was tested by whisper, Weber, Rinne and caloric tests. Rotation tests were discarded as superfluous. There were 40 instances of abnormal response to caloric testing, characterized predominantly by a delay in onset of nystagmus, induced vertigo and depression of the latter. The commonest abnormality was a delayed response on the side contralateral to the cranial injury. The main features associated with this delayed response were inner ear deafness, severity of injury, temporal site of the cranial injury, a closed type of injury and a history of otitis media. The main features associated with asymmetry of response were asymmetry of cranial or cerebral injury and asymmetry of deafness. "Central" responses were those productive of perverted nystagmus or abnormalities of past pointing and were present in 10 instances. They were associated with occipital, temporal, midline, bilateral and brain stem injuries, with bilateral deafness or otitis media. There was some relation between the caloric abnormalities and the duration of vertigo.

In the second group, comprising 14 cases, 7 of which had been included in the first series, hot and cold caloric tests were done with the patient in a supine position. In 9 cases there was directional preponderence, while in 7 this was toward the side opposite to the injury of the head.

Phillips concluded that disorders of vestibular function, as determined by caloric testing, were found in a high proportion of all cases of head injury and that in the severe cases focal lesions of the pathways from labyrinth to the cortex could be inferred. Vasomotor changes were thought to act as exciting stimuli for the symptoms of giddiness in most cases.

N. MALAMUD, San Francisco.

THE REHABILITATION OF PATIENTS TOTALLY PARALYZED BELOW THE WAIST, WITH SPECIAL REFERENCE TO MAKING THEM AMBULATORY AND CAPABLE OF EARNING THEIR OWN LIVING: II. CONTROL OF URINATION. DONALD MUNRO, New England J. Med. **234**:207 (Feb. 14) 1946.

"Every patient who has sustained an injury to the spinal cord, conus or cauda equina and is intelligent and cooperative has the right to expect infallible twenty-four-hour control of urination by the time he leaves his physician's care. Only those whose bladders have been denervated because of bilateral destruction of the parasympathetic plexuses or the lower four sacral segments or roots need any extraneous aid. Their numbers are negligible among civilians. Control of urination is an essential preliminary to self-support. No one will either walk abroad or be able to hold a job if he smells or if his clothes are wet with urine. There is no third choice between twenty-four-hour control with ambulation and self-support and a uriniferous aura with constant invalidism—usually in an institution—at the expense of the patient's family or the public.

"It is the purpose of this paper to present evidence that therapy of the proper kind, properly applied with perseverance and patience over a sufficiently long time, will assure this end result to all such patients. No discussion of the details of the technic of treatment will be offered at this time. This will be considered by itself in a subsequent communication."

The case material comprised a group of 125 patients who were selected from a series of 243 persons with injury to the spinal cord, conus or cauda equina. Every segment of the cord from the fourth cervical to the tip of the conus and all parts of the cauda equina are represented. One hundred and one of the 125 patients were chosen, first, because they had lived long enough—that is, one month or more—after the injury to permit some conclusions to be drawn as to the efficacy of the therapy; second, because a sufficient number of cystometrographic observations were made to verify the actual physiologic state of response of the bladder at frequent intervals; third, because all had become stabilized at the end point in so far as the genitourinary system was concerned. In addition, 24 patients in whom tidal drainage was either not needed or not used are included for comparison.

"Evidence is presented in support of the contention that every patient who has sustained an injury to the spinal cord, conus or cauda equina and is intelligent and co-operative can have infallible twenty-four-hour control of urination by the time he leaves his doctor's care.

"If tidal drainage is used at once after the receipt of the injury and supplemented by frequent cystometrograms, the chance of obtaining this result is 20 per cent greater than if its use is delayed.

"In a series of 101 cases selected from a larger group of 243 patients with injury to the spinal cord, conus or cauda equina, only 1 patient (0.9 per cent) in whom tidal drainage was properly used for a sufficient length of time failed to have infallible twenty-four-hour control of urination at the time of discharge."

GUTTMAN, Philadelphia.

Society Transactions

NEW YORK NEUROLOGICAL SOCIETY

Irving H. Pardee, M.D., *President, Presiding*

Regular Meeting, Dec. 3, 1946

Pain Disturbances Associated with Certain War Wounds. Dr. J. Lawrence Pool.

Brief descriptions of trench foot and causalgia were presented, and attention was directed to the burning or throbbing pain during the induction of spinal anesthesia that is referred to the lower extremity with a peripheral nerve injury. The pain in all these conditions is associated with vasomotor disturbance; it is increased with increased vasodilation and decreased as vasomotor stability is improved. It thus appears that some types of pain are related to circulatory changes. Observations in cases of causalgia suggest that circulatory disorders and the associated pain may in some instances be due to self-perpetuating activity within autonomic reflex arcs long after the precipitating pathologic process has vanished.

Dysesthesias associated with paraplegia may be affected by smoking and in some cases relieved by lumbar sympathectomy, suggesting that disturbances in the autonomic nervous system play a role in this type of distress. Headaches coincident with acute distention of the bladder in paraplegic patients are usually accompanied with mass autonomic discharge above and below the level of transection of the cord and are generally relieved as soon as the bladder has been drained. These observations suggest that such headaches may be due to widespread activity in the autonomic system, resulting in secondary vascular changes about the head. Relief is so rapid after drainage of the bladder that retention of toxic products scarcely seems the cause of these headaches.

Certain sensory alterations following posterior cordotomy and the fact that spinothalamic tractotomy usually does not afford relief of causalgia suggest that pathways other than the spinothalamic tract may transmit pain impulses—probably long intersegmental fibers in, or close to, the substantia gelatinosa.

Narcotherapy may relieve both the objective and the subjective components in some cases of causlgia, suggesting that self-perpetuating reflex activity may be beneficially interrupted at cortical, as well as at peripheral, levels of the central nervous system.

DISCUSSION

Dr. Harold G. Wolff: It is a privilege to discuss the work of a man who has been able to derive from a busy military experience provocative observations of the sort that Dr. Pool has reported tonight. The information on sensation which is needed to answer the questions he has raised is meager. From the point of view of the data Dr. Pool has presented, the deficiencies in information fall into two categories. First, it is not known precisely where afferent fibers from the leg, for example, enter the nervous system. Many afferent fibers from the leg enter with the first lumbar root, caudally. On the other hand, in order completely to sympathectomize a leg, it is necessary to resect at least as high as the ninth thoracic

spinal nerve root. It is conceivable, therefore, that some afferent fibers travel along with the sympathetic fibers to enter the dorsal roots at the ninth thoracic level, or perhaps even higher, but the ninth thoracic is a sensory level for the leg. Foerster, in his monograph on pain, written in 1927, described a condition like that which Dr. Poole reports, i.e., a transection of the cord at the twelfth thoracic segment, in which the patient was capable of receiving painful impulses when the leg was noxiously stimulated. Foerster suggested that a number of afferent fibers traveled with the sympathetic fibers, and perhaps came together in the midthoracic or the lower thoracic level. If this were so, we could understand the causalgia of the patient Dr. Pool desribes who had a section at the third thoracic segment, although her sensory level was actually at the twelfth thoracic. She had no trouble with her leg until the amputation, and then she began to have causalgia, which was relieved by sympathectomy. It is conceivable that she was receiving a certain number of impulses into the cord at a much higher level than the twelfth thoracic.

Dr. Pool, with respect to the persons who have pain during the first stages of spinal anesthesia, is it possible that this condition represents an initial irritant action, which then is followed by the analgesic action? In certain persons procaine is known to produce local tissue injury.

Dr. J. Lawrence Pool: Why was the causalgia on the side of the injury, a feature which was the peculiar part of this phenomenon?

Dr. Harold G. Wolff: That I cannot explain. Let us consider the pain which is experienced in parts separated from the nervous system by either nerve transection of local analgesia. Dr. Pool mentioned a man who had pain in the hand when the distal portion of the severed ulnar nerve was stimulated. Sir Thomas Lewis described an experience that might illuminate this observation. He placed an electrode on a cutaneous nerve that supplied the ulnar side of the hand and then blocked the proximal portion of that nerve so that when it was stimulated the patient experienced no sensation. Then he stimulated the nerve for several minutes. After a time the effect of the procaine disappeared, and then the patient complained of a burning sensation of considerable intensity in that portion of the hand supplied by the nerve which had been stimulated in its distal portion. In my opinion, this is not a satisfactory experiment because stimulation may have injured the nerve, and hence produced the pain. But Lewis tried to find support for his results in the work of others and came to the observation of Foerster, who, as you remember, made his demonstration of dermatomes by sectioning the dorsal root and then applying an electrode to the distal portion of the nerve. He observed that a portion of the skin became red and that this was the area in which the patient had pain when the central end of the nerve was stimulated. Foerster asserted that, although the nerves were separated from the nervous system by section, the patient experienced pain in the remote portions when the adjacent nerves were intact. When he sectioned the adjacent nerves, pain could not be elicited in this way. Lewis related these observations by suggesting a new type of peripheral nervous system. He suggested that there were fibers contained in the dorsal roots which had nothing to do with sensation as such, but which when stimulated caused to be liberated a substance in the periphery capable of stimulating pain endings from the overlapping adjacent nerves. This he called the nocifensor system, with fibers traveling with the posterior roots but having an entirely different, or nonsensory, function. This idea has not been popular; no one has ever been satisfied anatomically that there is such a separate system; but every one is convinced that it is possible to pick up a dorsal root, or even a cutaneous nerve, stimulate it and have vasodilatation at a distant

portion, and, when adjacent nerves are intact, have pain associated with the vasodilatation. These observations raise the question whether one must not look for a new kind of function. It may be that peripheral nerves when stimulated can elaborate a material in the tissue which is capable of stimulating other, adjacent, sensory nerve endings. If this is so, one may have an explanation of the phenomena presented by Dr. Pool. Dr. Pool stated that the patient had had the operation five to eight months before; it seems unlikely, therefore, that any dorsal root nerve fibers would survive. It could be assumed that autonomic fibers had grown into the tissues supplied by the ulnar nerve. Whether on stimulation of a sympathetic nerve fiber one liberates at the periphery a substance which is capable of giving rise to a sensation is at present not demonstrated, although it is true that acetylcholine injected intra-arterially does give rise to a burning pain.

It seems to me, Dr. Pool, that since you have made so many interesting observations and raised so many provocative questions, it is your responsibility to give us the answer to some of them. I should like to know, for example, whether your patient with the headache associated with the full bladder had a pressor response in the way a person who has his foot or hand plunged in ice water gets a pressor response. It is hard to believe that a man with his cord transected and no pain sense could have a pressor response from immersion of the foot.

Dr. Morris B. Bender: I enjoyed Dr. Pool's interesting and important scientific paper. While on duty at the United States Naval Hospital, San Diego, Calif., my associates and I had many patients with battle injuries of the peripheral nerves, spinal cord and brain. In our studies of these patients, we encountered many experiences similar to those cited by Dr. Pool. However, we did not have an opportunity to formulate our data, chiefly because our interest was directed toward disturbances in perception, especially visual perception. However, we agree with the theory that pain produced by injuries to the nervous system was in part due to a vicious circle, set up within the nervous system. This vicious circle does not necessarily involve the spinothalamic tract alone. The autonomic nervous system was considered to play a role in establishing this circle. Our neurosurgeon, Dr. Furlow, performed sympathectomies and sympathetic blocks in treatment of patients with causalgia. The patients were relieved by this method. As a rule, the patient remained well. However, if ony one of them was repeatedly examined with painful stimulation, the entire causalgic syndrome recurred. When this testing stopped, the causalgic pain subsided. Further testing again produced the syndrome. The most significant observation was that the pain syndrome could be abolished by sympathetic block and that repeated painful excitation induced recurrence. This suggested that causalgia is predominantly due to a dynamic, rather than to a structural, disorder in nerve function.

Dr. Thomas J. Bridges: Dr. Wolff suggested a pressor effect as a causative factor in cases in which headaches followed distention of the bladder due to an occluded catheter. My colleagues and I made careful observations on 2 patients at Bethesda, both with complete transections of the low cervical portion of the cord, and we could find only an increase in the pulse rate, of about 20, without changes in the blood pressure or the respiratory rate. We thought perhaps we were getting a renal back pressure, or evidence of a cardiorenal effect, but could find no evidence of such action. We had no explanation for the headaches.

Dr. Harold G. Wolff: The patients had headache?

Dr. Thomas J. Bridges: Yes.

Dr. Harold G. Wolff: But no pressor response?

Dr. Thomas J. Bridges: No.

DR. BENJAMIN ROSENBLUTH: For many years I have considered trigeminal neuralgia a deep pain, mediated through the cervical sympathetic nerves by way of the cavernous plexus. This plexus gives branches to the sphenopalatine ganglion, which is connected with the geniculate and other ganglia by way of the greater superficial petrosal nerve and the deep petrosal nerve, which form the vidian nerve. Bearing in mind the pupillary changes and sweating phenomena associated with cervical injuries and the deep tenderness in many cases of Bell's palsy, I considered the pain of autonomic origin. Though I know of no direct connection of the spinal root of the fifth nerve with the sympathetic system, I feel there must be such. Hence, I have for many years treated intractible trigeminal neuralgia by infiltrating the sympathetic locations in the neck, first with mild solution of procaine, followed by 50 per cent alcohol. At times I do this on both sides of the neck, as I think there is decussation, as evidenced by crossing of the ciliary reflex. I can report that at least 2 out of 3 patients are cured in this way, thus escaping further injections into the second and third branches of the fifth nerve or operation on the gasserian ganglion.

DR. HAROLD G. WOLFF: Will you say something as to why the pain in causalgia should be of the burning type? If causalgia is a disorder of a mixed nerve, containing fibers for superficial and deep pain, why are the pain sensations in the skin so acute? Lewis suggested that a chemical agent is liberated in the skin, which is poorly supplied with blood.

DR. J. LAWRENCE POOL: I cannot answer many of the questions that have been put. Obviously, a great deal of study is required along these lines.

I appreciate, Dr. Wolff, your helpful discussion of this subject of pain and of the mechanisms of the autonomic nervous system and the spinal cord involved. Your question regarding the pressor response Dr. Bridges answered in connection with his 2 patients.

I was glad to hear Dr. Bender's corroboration of some of these observations from his experience at the San Diego Naval Hospital; it is of particular interest that repeated examinations following sympathectomy may reproduce causalgia.

Dr. Rosenbluth mentioned the relief of pain by injection into the cervical sympathetic nerves, an observation which is in line with a pain mechanism due to involvement of the sympathetic nervous system.

I cannot answer all these questions but hope to investigate them further.

Disturbances of the Nervous System due to Anoxia and Related Factors in Flying Personnel. DR. WALTER O. KLINGMAN.

Physiologic problems introduced by high altitude flying came in for much attention during the recent war years. Indoctrination of air crew members and high flying combat and other missions resulted in states of anoxia in some persons, with disturbances in phyiologic functioning of the nervous system.

Despite careful selection of air crews and training, instances of anoxia occurred under the best of supervision. The incidence decreased as improved methods of control and technics were adopted.

Major physical changes occurring under conditions of high altitude are reduction in oxygen tension, increase in volume of gas-containing structures and decrease in solubility of gaseous nitrogen in the body fluids and tissues. These factors, singly or in combination, produce disturbances of the nervous system. Decided individual variations likewise exist with regard to withstanding these major changes.

Reactions resulting from anoxia are usually reversible by administration of oxygen if given in time, before permanent and irreversible changes in nerve cells occur. Certain persons, despite a supply of oxygen in the critical zones of high altitude, experience temporary or transient changes. These symptoms include disturbances of equilibrium and coordination, impairment of motor or sensory tracts, disturbances of consciousness, amnesia, confusion, disorientation, dyskinesia, aphasia, migraine-like headaches, scotoma, urticaria, neuralgia, blurred vision, nausea, generalized muscular weakness, interference with depth perception, paresthesias and syncope. Some of these reactions are also observed after flight and are not immediately or shortly relieved by continued administration of oxygen.

Syncopal reactions of vasodepressor character and syncope of the nondepressor type are commonly observed during adaptation to high altitude conditions, usually in the presence of multiple symptoms of decompression sickness such as bends and chokes. The mechanism of the vasodepressor reaction is presumably through afferent stimuli arising from various sites affected by decompression sickness, together with psychologic factors associated with the situation. Reactions of the nondepressor type may result from hypertension and tachycardia in early anoxia, reflex central causes or vasospastic phenomena.

The finding of a predisposition to migraine or migraine-like attacks in the past or the family history suggests that the syndrome and clinical migraine may be similar in their origin—spasm of the cortical cerebral arteries.

The effects of acceleration and deceleration, during rapid change of direction, may produce cerebral anemia, and possibly structural damage to the brain when of severe degree. Unconsciousness may occur with impairment of other cortical functions, convulsive movements of the limbs having been experienced by some, and there may be retrograde amnesia and disorientation.

The unusual environment of repeated or long exposure to sudden changes of altitude, together with the great strain to which flying personnel are exposed, may result in definite psychosomatic complaints, producing chiefly a chronic fatigue not explainable wholly on the basis of physical stress. Emotional factors also play a considerable role in the development of such states. Undoubtedly, the diffuse damage to tissue which occurs in repeated decompression sickness may also upset the homeostatic mechanisms concerned in the reparative process and eventually lead to fatigue or prolong the fatigue of emotional stress.

DISCUSSION

DR. HURLEY L. MOTLEY: It may be of interest for me to relate a few of my experiences in indoctrination work in the low pressure chamber and to describe some of the acute reactions. Dr. Klingman saw the patients he described after they had left the low pressure chamber, at a time when most of the acute reactions had subsided. Some of the reactors had no symptoms at the time of the low pressure run, but symptoms developed later. All the trainees were instructed to report to the hospital if any unusual symptoms developed, because there was no way of predicting whether they would or would not develop. The indoctrination of the trainees was of real value to the Army Air Forces in reducing accidents, particularly those from anoxia. The development that was made in designing new oxygen equipment was remarkable, and some of this apparatus is adaptable for clinical use. Engineers in the Army Air Forces have repeatedly been farther ahead in the designing and performance of planes than in solving the medical problems resulting for the man. The performance of the plane is limited by what the man can stand, as borne out repeatedly in high altitude flights, changes during acceleration and many other aspects. Airplane designers often give little consideration to the pilot. To illustrate: The size of the cockpit in some of the fighter

planes was so small that the pilot had to be lifted out after a long flight because of fatigue from the cramped space. "Pilot black-out" also demonstrated that the performance of the plane was limited by the human element. A notable advance was made by medical scientists in the development of the pressure suit, called the "G" suit, to help prevent black-out. This suit consisted of five bladders, one each over each thigh and calf and over the lower portion of abdomen. Pressure in the bladders applied at the time of a change in direction helped to keep the blood pressure up and thus prevent black-out. These suits were used by pilots of the Ninth Air Force very successfully, with a definite increase in "G" tolerance, enabling better maneuvering of the plane. The human centrifuge demonstrates vividly the effects of "G" force on the body, and it is used in perfecting protective devices, such as the "G" suit and indoctrination. The jet planes go so fast that it is impossible for the pilot to get out unaided if an emergency arises. This problem was solved by designing an automatic device to shoot out both the pilot and the seat by means of compressed air.

It was thought at first that men susceptible to decompression sickness could be eliminated with one run. The first low pressure chamber runs were severe and consisted in taking the trainees to a simulated altitude of 38,000 feet (12,000 meters) and keeping them there for three hours. Many severe reactions developed. Later it was found that one low pressure run would not eliminate the group susceptible to decompression sickness, and the time at 38,000 feet was reduced to one hour, a less severe test. Later still, the standard run was 30,000 feet (10,000 meters) for one hour and 38,000 feet for fifteen minutes. These simulated flights were realistic. The trainees were instructed primarily how to take care of themselves at high altitude, with emphasis on the use of oxygen and the oxygen equipment. Constant supervision was maintained when men were in the chambers by trained technicians watching at all times for any unusual symptom to develop. If the subject was at all familiar with the low pressure chamber, there was no fear; but persons coming in for the first time usually experienced definite apprehension. This fear, I might add, was probably more pronounced among physicians than in any other group.

As Dr. Klingman has pointed out, the rewards of better indoctrination were shown statistically in the latter days of the war. In 1943 all flying personnel were required to receive altitude flying training. It was amazing to learn how many of the older flying personnel thought the use of oxygen was unnecessary for altitudes up to 20,000 feet (6,600 meters) or even 25,000, feet (8,300 meters). Others thought the use of oxygen for short periods (five to ten minutes) adequate. The symptoms of anoxia are insidious; there is no pain or warning signs. Demonstrations were designed to impress the men that they could not depend on their own feelings for detecting anoxia. One of the demonstrations consisted in using one of the men, a volunteer, as a guinea pig. He was usually asked to write during the test. After the oxygen was turned off at 30,000 feet, his writing gradually became unintelligible. The rest of the personnel observed this subject closely. He had no pain; yet unconsciousness developed quickly. At least 50 per cent of the volunteers never knew they were unconscious; yet the condition was obvious to the others. When the oxygen was turned on, the subject was fully conscious in less than thirty seconds. If he was writing when he passed out, he started writing again when he came to. Whatever the man was doing when he passed out he resumed when he came to. Another stunt was for a volunteer to try to take off his shoes and socks and put them back on without oxygen. He could not do this at 30,000 feet, but many men thought they had, for, again, they were not aware that they had passed out. All trainees had a chance to see these

demonstrations showing that at high altitude the proper use of oxygen and the oxygen equipment was necessary in order to stay alive.

Subjects who had bends during one run were more likely to have symptoms on a second run. However, four or five runs were required to select a resistant group to decompression sickness. Time did not permit giving all cadets four or five low pressure chamber tests. At the peak of the air crew training program, 400 to 500 cadets went through the altitude training unit at Maxwell Field, Ala., each day. There were no deaths at this field in training over 100,000 men. We were fortunate in this respect. Even with all safety precautions observed, a death occurred at another field from reaction to the altitude chamber "flight." The trainee became unconscious after about fifteen minutes at 30,000 feet, and he was taken to ground level rapidly. Unconsciousness persisted despite all treatment, and death resulted from pulmonary edema after approximately thirty-six hours. Nothing specific was observed post mortem. Before autopsy, a ruptured aneurysm in the brain was thought the most likely diagnosis. A small number of trainees with claustrophobia were eliminated at the time of the chamber flight. Another group, of fainters, classified as having vasomotor instability, were not qualified to be flying personnel and were usually eliminated by the low pressure run. Permanent defects of the ears or sinuses were detected. The malingerers were easily shown up in the low pressure chamber. Some had the idea that they could not fly above 10,000 or 12,000 feet (3,300 to 4,000 meters), or perhaps they did not want to go into combat and could not fly at high altitude. This group was tested in the low pressure chamber with the altimeter covered, so that the true altitude was unknown. We might take them to 30,000 feet and keep them there an hour, but they might be informed that the altitude was 5,000 feet (1,300 meters). It is impossible for even an experienced personnel member to tell the pressure altitude in a low pressure chamber when he has on an oxygen mask.

All possible safety precautions were taken with low pressure chambers with the twenty men inside. Two trained technicians were watching the trainees from outside through portholes, and another man, who lectured, also watched constantly. Frequently an oxygen mask would loosen and the subject would have a leak, and he might pass out from anoxia. We believed that most of the symptoms from exposure to high altitudes were due to nitrogen bubbles forming in the tissues of the body (blood, muscles, tendon sheaths or brain). When the existing pressure is reduced by one-half, bubble formation begins. Pain around large joints is commonest (bends). In the pulmonary circulation the symptoms from the nitrogen bubbles are called "chokes." The nitrogen bubbles may interfere with an adequate oxygen supply to the brain, and symptoms of anoxia may develop, even with 100 per cent oxygen. The bubbles get larger the higher one goes, and the reactions are apt to be severer at 30,000 than at 20,000 feet. Thirty thousand feet is a dividing line for man, as in general the reactions that occur are usually mild below this level and are more likely to be severe above. If 100 per cent oxygen is used a few minutes before ascent to altitude and all the way up, some of the nitrogen in the body is washed out. If all the nitrogen is washed out before ascent to 30,000 or 38,000 feet, there should be no symptoms. This method is impractical, as six to twelve hours is required to wash out all the nitrogen. However, breathing 100 per cent oxygen as described, even for a short time, will reduce the incidence of decompression sickness to a low figure.

The immediate treatment of acute reactions to reduced pressure consists primarily in three things: (1) Recompression to ground level should be made as rapidly as possible; (2) the patient should be given 100 per cent oxygen all the way to ground level and kept under treatment with oxygen until the acute symp-

toms subside, and (3) he should be kept at rest in bed for at least one hour, or longer if necessary. The blood pressure and pulse should be normal before the man is released. If any symptoms persist beyond two hours, the subject should be sent to the hospital for observation and for rest that night and the next day, if necessary. Some of the symptoms are very severe. Rapid collapse with shock and unconsciousness; convulsions; transitory paralysis of various parts of the body, and spots, scotoma and partial blindness in the eye may occur. Bradycardia, with a low blood pressure, particularly the diastolic, was almost always present. No permanent damage was observed in the trainees. The acute symptoms usually cleared rapidly. Reactions involving the central nervous system were most likely to have residual signs, which might persist for many days, but eventually cleared.

Dr. Henry A. Riley: I understood from Dr. Klingman's presentation that the mental and physical changes described were due to lack of oxygen and anoxia. It is therefore difficult for me to understand why these symptoms are present in patients who are breathing 100 per cent oxygen.

Dr. Walter O. Klingman: In many instances, for the period in which the experiment was carried out, the oxygen mask was not applied until the subject reached an elevation of approximately 18,000 feet, and during that period we saw a great many more reactions than when we started with administration of oxygen at a much lower level. In other words, a partial anoxia existed before the subject reached 18,000 feet (6,000 meters). Then, when he was carried to 30,000 feet, although 100 per cent oxygen was given, the oxygen saturation of the blood may have been materially reduced. That plan was later abolished, for we were having a fair number of reactions, and the oxygen mask was applied at a level lower than 18,000 feet.

Nutritional Disorders in Allied Repatriates and Japanese Prisoners of War. Dr. William H. Everts.

The scope of this paper is entirely clinical and represents my observations on the physical and neurologic status of some of the allied repatriates recently removed from Japanese prison camps in Japan and China to American Army hospitals in Saipan and the Philippine Islands, as well as of Japanese prisoners of war in the Prison Hospital at New Bilibid and nearby prison stockade after the Japanese surrender.

The first repatriates examined were 75 American soldiers removed from Japan and hospitalized in Saipan. These troops had been imprisoned since the earliest hostilities in the Pacific, first in the Philippines and later in Japan. Histories taken from these men were extremely similar, and the various presenting disorders occurred uniformly at about the same time. The diet during imprisonment had always been low in calories; dietitians' estimates were 800 to 2,000 calories, with the usual diet furnishing about 1,500 calories. The diet was never adequately balanced, since it was regularly low in proteins, fats and vitamins and always high in starches. The staple was rice, with yams, leafy vegetables and oil (coconut). Little meat or fish was ever in their diet, and fruit was rarely obtainable. This diet was the same for every one, and was thus especially inadequate for those who had to work and for men of above average stature. The larger men had suffered more in general, and more often died when sick, than did the men of small stature.

Chronologically, the earliest disorder described by these troops was the progressive, severe loss of weight, and in four to six months many noted swelling of the feet and ankles. This swelling varied in degree, and at times disappeared.

There were also general lassitude and ease of fatigue. In the first year many men noted sore mouths and swollen gums (scurvy); others had painful fissures at the angles of the mouth (riboflavin deficiency). Many, too, described burning feet and told how they could barely walk because of the pain and burning in the soles of their feet. In some, the burning feet appeared to be an isolated phenomenon; in others, it appeared to be but an accompaniment or a prodrome of dry beriberi, since there developed progressive, symmetric, ascending evidence of neuritis, described in somewhat the following chronologic order: The feet grew heavy and ached, and shooting pains and persistent burning then developed in the soles. These pains often ascended to the knees, and might later affect the hands and forearms as well. In many cases of the latter type visual symptoms, first dimness and later varying degrees of blindness, developed.

That pellagra was also common was evident from their description of sore mouths, and swollen, painful and reddened hands and feet or other exposed parts.

Far commoner, however, was the swelling of the feet and ankles by day, and of the face each morning—a dependent type of edema, which might become very severe and produce great swelling in the scrotum and abdomen, completely incapacitating the men. With this was described severe nocturia, with micturition twelve to fifteen times during one night.

These disorders were always made worse, or at times precipitated, by malaria, dysentery or infection with worms, all prevalent in the Pacific Ocean area.

These men are now responding well, for the most part, on a purely supportive regimen of adequate diet and vitamins.

It is of interest that many of the troops who had been free from edema and had only minor distress in their feet, and who had been ambulatory prior to embarking from Japan, had severe edema of the extremities, and a few became almost paralytic, en route to Saipan on warships when they were permitted to satisfy a voracious appetite during their week at sea. Some of these men subquently became severe therapeutic problems. Likewise, in the hospital it was early apparent that these starved and physically wasted men could not tolerate full diets; less well did they tolerate large blood transfusions, even though some were anemic and had a low protein content of the blood. Hence, it became the practice to feed the sicker of these patients according to their weight plus 15 per cent, give multivitamin capsules and reserve small transfusions for the men with the severest malnutrition. Their course as a rule was good, and in about ten days they could tolerate a regular diet and gained strength rapidly. All the troops I saw here had had an improved diet for three or four weeks before arriving in the hospital, for it had been dropped to them by air since Aug. 16, 1945 and they had been one week at sea.

Both the American and the British repatriates gave the history of a diet deficient in calories and seriously deficient in protein and all water-soluble vitamins, viz., vitamin B complex and vitamin C, and, to some extent, in the fat-soluble vitamin A. This severe dietary deficiency early became manifest in malnutrition and dependent edema, followed only after a few months by the evidences of vitamin deficiency. Early among these were sore, hypertrophied gums, due to lack of vitamin C; fissured angles of the mouth, due to lack of riboflavin; acute symmetric dermatitis and the sore mouth of pellagra, due to lack of nicotinic acid, and, later, the manifold symptoms of beriberi neuritis, due to lack of thiamine chloride. Early, too, was the frequency of "burning feet," probably related to vitamin B deficiency. The prompt response of early visual symptoms to administration of vitamin A warrants its inclusion with the probable vitamin deficiencies.

Both the malnutrition and the vitamin deficiency were frequently aggravated by disease, poor living conditions and the frequent added burden of physical work. All these made for a picture of starvation and disease rarely observed and experienced in modern times.

After the recapture of Manila and the Japanese surrender, great numbers of starved, wounded and otherwise sick Japanese troops became the responsibility of the Medical Department of the Army of the United States. These sick and wounded were initially hospitalized at New Bilibid (Philippine Commonwealth Prison), where soon the facilities were greatly overtaxed with over 4,400 bed patients. Later the men were moved to newly constructed buildings in a nearby prison camp, by which time the hospitalized sick census rose to over 6,000 patients, the great majority of whom were medical. There were additional great numbers of ambulatory Japanese prisoners, who, too, showed advanced grades of malnutrition, many with dependent edema; these men were managed on a regular prisoner status by the military police.

The Japanese soldier, conscripted for the most part from the peasant and fisherman classes, is short, with an average height of 5 feet 3 inches (160 cm.), a long torso and short, relatively thick arms and legs. His discipline was largely one of literal, unthinking, blind obedience. Thus, generally good cooperation was easily obtained from the Japanese in the care of their sick, who, in turn, seemed appreciative of whatever was done for them.

There was little stirring under this vast tentage at New Bilibid; cots by the thousands were occupied by these small, wasted men, many with ulcerous, edematous extremities and protuberant bellies. The apathy, the stench of the sick, the frequency of death—the last a very public affair—lent much of a depressing nature to an already appalling medical problem. Later it was possible to improve both the management and the morale of the patients and personnel in general by removal to the new hospital.

Interrogation of Japanese army physicians from both forward and rear echelons yielded the following data: "The Japanese soldier's normal diet consisted of three canteen cups of rice, plus meat or fish, each day. Yams and other vegetables were regularly available. Some cheese was frequently obtainable. Much of their food was of cold storage type and entirely adequate. Medicines, too, were always available in ample quantity."

The health of the Japanese soldier was good until late in December 1944 and January 1945, after which time it declined seriously. The blockade of the Philippines was in effect for a full year before V-J Day; but, though their own food supply failed them, they were able to "live off the land" until the American invasion drove them into the mountains. Here they subsisted on leaves, grass and roots. No meats, fish, rice or fats of any kind were obtainable. The sick and wounded could not be cared for, and many died. Many others became sick and died either of inanition or because they were too weak to recover from other, intercurrent, illness. Medicines ran out, leaving them without means of combating the then rampant malaria and dysentery. These physicians brought out that whereas beriberi was common in Japan, it was rarely accompanied with inanition. Thus, they regularly recognized three types: the dry, the wet and the mixed. The dry type usually came first, then the mixed; and it was the mixed type which was usually seen by the physician.

Among their troops, wasting of the body was severe as a rule, and it became difficult to tell whether it was severe malnutrition or beriberi which the patient had; the two were always associated later.

The earliest symptoms of beriberi in this group of patients were usually aches and pains in the body and extremities, fatigue and often some hyperesthesia

over the anterolateral surface of the legs (distribution of the peroneal nerve), in the area of the antecubital fossa and extending up and down in the distribution of the medial and lateral antebrachial cutaneous nerves. The first phase passed into hypesthesia and hypalgesia, often with accompanying tinnitus and mild deafness (vision never affected), and in three to four weeks systemic effects developed with swelling of the ankles, cardiac enlargement and often ascites and fluid in the chest. Many of these patients died suddenly of cardiac failure. A few became delirious, and a few psychoses also occurred. Frequently, also, malaria or dysentery complicated the beriberi and malnutrition—thus, the morbidity and mortality had been very great prior to capitulation.

From the standpoint of treatment, these patients received a moderately well balanced diet of 1,200 to 1,500 calories, with multivitamin capsules and occasionally the addition of 10 mg. of thiamine chloride each day. Malaria and any other disease received treatment accordingly. The response of these patients was uniformly good, except for some with cardiac disease, many of whom died suddenly.

As soon as these patients were ambulatory, free from edema and gaining weight, they were transferred to the regular prison stockade and maintained on a regular prison regimen.

There was, in addition, a group of about 100 wives of Japanese soldiers, 35 infants and a few older children. Malnutrition of moderate to very severe grade was present in all. The nursing infants were cachectic and had obvious vitamin deficiencies, consisting of infantile beriberi, scurvy and, especially, cheilosis. The mortality among these infants was great; the majority died in a few weeks. The older children responded more like the adults with respect to their nutritional state, and many showed gradual improvement, as did the majority of the women, on an improved dietary regimen.

The Japanese group, then, showed what may be regarded as borderline acute starvation from the standpoint of vitamin adequacy, not only in the Philippines but also in their homeland. The picture was regularly one of severe malnutrition with evidences of hypoproteinemia and varying grades of deficiency in the vitamin B complex and in vitamin C. In addition, this group was ravaged by the usual diseases so prevalent in this area, malaria and dysentery.

Specific diagnoses were often difficult to establish because of the many mixed pictures and, to no little extent, the paucity of laboratory facilities available at that time in the prison hospital.

One limited study showed clearly a high incidence of moderate to severe degrees of secondary anemia, and plasma protein levels were often well below the critical level for edema.

Transfusions were given to many; but here, again, the larger transfusions resulted in the sudden death of some patients, and so smaller ones were resorted to. Vitamins in the form of multivitamin capsules were regularly administered. The diet was never excessive, so that overfeeding did not enter the problem.

DISCUSSION

DR. MURRAY GLUSMAN: I was particularly interested in the manifestations of deficiency Dr. Everts described in the Japanese who were captured after the American invasion of the Philippines. He mentioned ataxia, tinnitus and decreased hearing as evidences of nutritional deficiency in the Japanese troops. These phenomena were unusual in the allied personnel captured earlier by the Japanese. Similar phenomena, however, were observed by Spillane and Scott in German troops captured in the Middle East (Spillane, J. D., and Scott, G. I.: Obscure Neuropathy in Middle East: Report on 112 Cases in Prisoners-of-War,

Lancet **2**: 261-264 [Sept. 1] 1945). These authors noted the development of decreased hearing, tinnitus and ataxia in association with retrobulbar neuritis in German troops.

Dr. Everts described the nutritional disorders he observed in allied personnel who were being repatriated from various Japanese prison camps. It may be of interest, therefore, to mention the diet on which many of these prisoners of war existed and to recount briefly some aspects of the various deficiency syndromes as they first developed.

At the Bilibid hospital in Manila, the central hospital for prisoners of war on Luzon, the daily diet issued by the Japanese consisted of about 500 Gm. of rice, 200 to 250 Gm. of vegetables and small amounts of coconut oil and salt. At times the rice was well milled; at other times it was undermilled. The vegetables were usually leafy greens. From time to time a negligible amount of meat or fish was added to the diet. The rice was either steamed or cooked into a gruel, and the vegetables were always boiled. This diet, which was supplemented with various small purchases from the commissary operated by the Japanese, was also more or less representative of what troops captured by the Japanese in Hong Kong, Singapore and Java received.

Except for loss of weight, perhaps the first evidence of nutritional deficiency which appeared in the American troops in the Philippines was edema. This developed about the time of the fall of Corregidor, in May 1942, and soon became prevalent. In some cases the edema progressed to ascites, and in a few instances signs of cerebral edema developed.

Another early manifestation was loss of libido. This, too, was first noted about the time of the fall of Corregidor. It is for the psychiatrists to relate this fact to the rather low incidence of psychoses among the prisoners of war. Cases of conversion hysteria were not infrequent. In Japan in 1945 they were seen in increasing numbers; however, true psychoses were not common.

In July 1942, pellagra began to appear among the prisonsers of war in the Philippines, and in a relatively short period the rashes, glossitis and diarrhea of pellagra became common findings. Only an estimate of the incidence of pellagra can be given; however, it would be safe to say that at Bilibid during the winter of 1942-1943 at least 30 to 40 per cent of the patients admitted for all causes showed some evidence of pellagra. Dulness and impaired memory were often associated with pellagra. Disease of the spinal cord, however, which could be definitely attributed to pellagra, was not apparent. The response to nicotinic acid therapy of the rashes, glossitis, diarrhea and mental symptoms associated with pellagra was gratifying.

Signs of ariboflavinosis appeared in the summer of 1942, and angular stomatitis and scrotal dermatitis soon became common.

Dr. Everts mentioned night blindness in the British prisoners of war. This was the first of the ocular manifestations of nutritional deficiency to appear in the Philippines. Somewhat later, corneal ulceration became a fairly common and troublesome complaint. Nutritional amblyopia, however, was one of the most important problems of nutritional deficiency seen in the Philippines. This condition was associated with central and paracentral scotomas and was probably due to retrobulbar neuritis. It first appeared in Bilibid in the late summer and the fall of 1942, and it attained maximum incidence in 1944, at which time rations were particularly poor and a very considerable percentage of the patients and staff were affected.

In the late fall and the early winter of 1942 a major epidemic of "burning feet" appeared at Bilibid. This became a serious and puzzling problem. A good

deal of discussion went on among the medical officers who encountered this condition as to whether or not it was a manifestation of beriberi. However, the pains in the feet did not respond to thiamine chloride, and patients with "burning feet" did not lose their deep reflexes in the lower extremities or have muscular paralysis. In some patients with "burning feet" who were transferred to Japan gangrene of the distal portions of the feet developed. This probably indicated vascular impairment associated with the condition.

A good deal of "wet beriberi" was seen in the Philippines. How much of this was due to hypoproteinemia or starvation edema is difficult to say. My unit was equipped to do blood protein studies, and on clinical grounds alone the differential diagnosis is a difficult one.

In Japan proper, at the Kobe hospital for prisoners of war, the deficiency syndromes generally were not so clearcut or so severe as those seen in the Philippines. This may have been due to the fact that in Japan variable amounts of barley, millet seed and soy beans were always mixed with the rice issued to prisoners of war. Of particular interest in Japan were the common complaints of nocturia and polyuria. It was not infrequent to find patients who complained of having to void ten or twelve times during the night. These complaints were apparently due to a disturbance of water balance. They were not associated with glycosuria or infections of the genitourinary tract.

Not all the manifestations of nutritional deficiency which appeared among the troops captured by the Japanese can be explained in the light of present knowledge of avitaminosis and nutritional deficiency. It is possible that some of the atypical manifestations may have been due to deficiency of one or more of the newer vitamins, for which deficiency syndromes have been described in experimental animals, but not in human beings.

Dr. Henry A. Riley: There is little I can discuss in this paper, for I had no opportunity to examine any of these patients. I, therefore, have had no first hand experience to compare with that of Dr. Everts. The whole paper was of extreme interest to me as a description of the conditions which he saw. The only patient with whom I had any contact was a correspondent, Mr. Powell, who was interned by the Japanese in the early days; he lost both his feet and had an extreme deficiency syndrome. I examined him when he was at the Presbyterian Hospital for a prolonged period, with the diagnosis of peripheral neuropathy. I was asked to see him because of a complication which arose in the course of his convalescence, the reason for which was not evident, namely, the sudden development of massive ataxia, which made it almost impossible for him to carry out any of the tests for coordination in the upper and lower extremities. He had almost complete loss of all the deep sensibilities, and it seemed as though the dorsal columns and the adjacent portions of the cord had been temporarily put out of function. The only additional factor found in the examination at that time was an extreme change in the blood volume, not in the actual constituents of the blood, since the ordinary blood count showed no material change, but a steep drop in the blood volume. His improvement began as soon as that was discovered and adequate means taken to reverse this condition.

I should like to ask whether the evidences of involvement of the central nervous system improved at all as compared with the improvement in the signs of damage to the peripheral nervous system. In most patients who present the classic signs of dorsolateral degeneration dependent on blood dyscrasias, the dysfunctions of the central nervous system do not change much if they have been in existence for any length of time. What does improve is the dysfunction due to associated involvement of the peripheral nervous system.

DR. WILLIAM H. EVERTS: In reply to Dr. Riley's question about improvement of the central nervous system: First, the time element during which we had to observe these patients was too short, but I may say there was pronounced improvement in strength and in the numbness of the feet and legs, as well as in the vision of some of them. The acuity of vision which they had remained, but there was practically no improvement in the central scotomas. The period of observation, during which the diets were better, was about seven weeks. For the first four weeks we did not see them. They had food dropped by airplane, and the diet was thus improved; but, according to many, it was not adequate. In the hospital the regimen was adequate, but neither the scotomas nor the symptoms referable to the cord improved during the time of observation. As I was observing them, I felt that the improvement recorded on many of the charts was purely that of general strength, of the peripheral nervous system, and not that of the central nervous system at all. In the course of a few weeks these men were ready to get up and be on their way, and they hiked off to the ships of the British army and to our ships without too much trouble. That was not so with the men who were serevely ill, and I think they will be permanently crippled.

PHILADELPHIA NEUROLOGICAL SOCIETY

Anthony S. Tornay, M.D., *Presiding*

Regular Meeting, Feb. 28, 1947

Pneumoencephalographic Diagnosis of the Presenile Dementias. DR. PAUL CHODOFF (by invitation) and DR. WALTER FREEMAN, Washington, D. C.

The literature relating to the value of pneumoencephalography in the differential diagonsis of the presenile dementias was reviewed. The report of Flugel indicating that the extracortical air is distributed as large, confluent masses over the frontal lobes in cases of Pick's disease and as broad stripes over the convexity in cases of Alzheimer's disease was shown to be based on rather tenuous evidence. Nine cases were reported, in all of which pneumoencephalograms had been made and in 8 of which autopsy had been performed. The pathologic observations were compared with the pneumoencephalographic findings, and it was pointed out that the lack of clearcut pathologic distinction between Pick's and Alzheimer's disease vitiates the value of air studies in the differential diagnosis. Uniform or asymmetric ventricular dilatation without displacement was found in all the 9 cases reported. In these cases the appearance of the extracortical air was of little or no value in differentiating the two conditions. It was concluded that the pneumoencephalogram is a valuable diagnostic aid in distinguishing the presenile dementias from other conditions, but that it is of little or no value in differentiating the various members of the presenile group.

DISCUSSION

DR. WALTER FREEMAN, Washington, D. C.: Dr. Chodoff might do well to bring out in his final discussion that pneumoencephalographic examination in these cases is not always without risk. I recall a patient, not in this series, who after pneumoencephalographic examination went into profound shock and was saved only by heroic efforts, including a blood transfusion and oxygen inhalations. Another patient, who probably had unrecognized septicemia at the time the procedure was carried out, died of meningitis. Autopsy revealed that the ventricles were filled with a mixture of air and pus.

The sections in 2 of these cases were particularly interesting. One is accustomed to the picture of Alzheimer's disease and, to a less extent, of Pick's disease, which is less common. However, the patient with the largest ventricles of the series, and who later went into status epilepticus, showed a widespread demyelinating process in the subcortical white matter. It was not accompanied with an inflammatory reaction. There was not much sclerosis. The white matter simply disappeared.

The basal ganglia were exceptionally small. However, there were no disseminated plaques throughout the rest of the nervous system. The cerebellum also showed demyelination. In the last case the brain showed the changes neither of Pick's nor of Alzheimer's disease, and only a moderate degree of arteriosclerosis. Perhaps Dr. Chodoff can say more about the mental phenonema in this case, for the cortex and the subcortical white matter, except for the dilated ventricles, appeared to have been in a rather satisfactory condition.

Dr. Charles Rupp: I wonder whether the authors observed anything characteristic in the pneumoencephalogram that would assist in differentiating the so-called presenile psychoses from the arteriosclerotic type.

Dr. Michael Scott: I should like to ask Dr. Freeman and Dr. Chodoff what type of anesthesia they used and whether they carried out complete drainage during the encephalographic procedure. Finally, in what position were the patients placed when the air was introduced and the roentgenograms were taken?

Dr. Matthew T. Moore: The authors are to be congratulated on bringing up once more the use of pneumoencephalography in differentiation of the organic and the so-called functional psychoses. In 1933 and in 1935 I reported a series of 152 cases representing various types of psychoses. At that time, I demonstrated in cases of schizophrenia a type of atrophy involving the frontal and parietal lobes. The brains in the first and third cases of that series have recently been studied pathologically. In both, the gross morbid changes reflected the original observations in the air studies.

It must be kept in mind, however, that the air findings, as shown by Dr. Chodoff, are not specific for any one disease. For example, I have seen a case of dementia paralytica in which the encephalogram would duplicate that in his first case. The enlarged lateral ventricles present in several of the other cases shown here are frequently seen in cases of cerebral arteriosclerosis.

I wish also to ask whether the authors use ether anesthesia. This may cause cerebral congestion and edema and prevent dispersion of air. What has been the time elapsing between the performance of the pneumoencephalographic study and the autopsy?

Dr. A. M. Ornsteen: This presentation moves me to talk briefly about the practical aspect of the post-traumatic encephalogram. It has been the experience of a number of us to be confronted with vexing problems of the postconcussion syndrome. Encephalograms have been produced to prove the contention that there is cortical atrophy. The validity of the roentgenologic basis, I must say, is often highly questionable. This evening's presentation makes the value of the post-traumatic encephalogram all the more questionable, since the films in cases of Alzheimer's and of Pick's disease, in which the cortical atrophy is known to be extreme, do not show the wide markings of the cortical fluid pathways considered, in the opinion of some clinicians, to be *sine qua non* for postconcussion cortical atrophy. After hearing this paper and viewing the encephalograms shown by Dr. Freeman and Dr. Chodoff, one should be more conservative in interpretation of post-traumatic encephalograms.

DR. F. H. LEWEY: In some of the ventriculograms the basal ganglia were poorly outlined. Is there a reason for it?

DR. BERNARD J. ALPERS: I enjoyed this paper very much. The approach of Dr. Freeman and Dr. Chodoff in regard to the problem of presenile psychoses has been very much that of the rest of us. There arises the question why it became necessary to make the pneumoencephalographic studies in these cases, wholly apart from the desire to see what the brain might look like in an encephalogram.

From the standpoint of diagnosis, I should say that on the basis of the experience of my colleagues and myself, and we have had experience with several cases of this sort, it has been necessary to make encephalograms only when a diffuse cerebral process had to be differentiated from a possible cerebral tumor. From the abstract of these cases, I should say that the diagnosis of presenile dementia seemed to be clear enough. There were definite indications of deterioration and other evidences of a diffuse cerebral process. The problem, therefore, resolves itself into the question whether an encephalogram can be regarded as useful in the diagnosis per se of a presenile dementia and, if it is not useful, what it is useful for. I do not think it is useful in the diagnosis of a presenile dementia. Our main use of the encephalogram in cases of the presenile dementias has been in determining whether there was a diffuse cerebral process or a cerebral tumor. I remember a case of a man with a typical picture, or what seemed to be a typical picture, of Alzheimer's disease; he had a great deal of mental deterioration and was in the presenile stage; autopsy revealed a cystic tumor of the cerebellum. I remember distinctly another case, that of a woman, who also had a typical picture of presenile dementia; in the course of time there developed choked disk and evidence of a glioblastoma multiforme. I should say that pneumoencaphalography seems to have relatively little value in the actual diagnosis of a presenile dementia, but that it has great value in the differential diagnosis of a presenile dementia and some other process, such as a cerebral tumor.

DR. PAUL CHODOFF, Washington, D. C.: I thank all the discussants for their observations. Dr. Freeman brought up the question of injurious effects of the encephalographic study; in 1 case the result was certainly bad. One of the patients had his encephalographic examination, never really recovered, went into hyperpyrexia and died in a few days. In another case there was considerable reason to believe that the encephalographic procedure had hastened the end. Of course, all these patients were deteriorated. Dr. Rupp asked about the value of the encephalogram in the differential diagnosis of the presenile and the arteriosclerotic encephalopathies. My feeling is that it is of no value—that the amount of atrophy is not mirrored precisely enough by the air studies for anything differential to be determined. Actually, in some cases, arteriosclerotic encephalopathies occur in cases of presenile age distributions, and in these cases the air encephalogram would be of little diagnostic value.

Dr. Scott asked the question which I was waiting for—about the technic of the air studies in these cases of presenile dementia. The data were collected from the patients' charts at St. Elizabeths, and none of the encephalograms were made personally. In most of these cases, unfortunately, the amount of fluid removed and of air replaced were not mentioned. However, I got as much information as I could from the people who had been working there, and I believe that in all cases the attempt was made to drain the spinal fluid entirely; I am further led to believe that because during the period in which these procedures were being carried out it was common practice to take all the fluid one could get, in contrast to present custom. No anesthesia was used. The studies were all made with the patient in the sitting position. So far as the cases of Schilder's disease are

concerned, 1 of the 2 cases—the outlandish one—did not fit into any particular category; it may have been an instance of Schilder's disease, but that is the only one in which this diagnosis seemed possible.

Dr. Ornsteen's comments on the encephalogram in his case are pertinent. Dr. Lewey asked about atrophy of the basal ganglia. The case reports read were abstracted from a considerable mass of material, and in a number of the cases there was considerable atrophy of the ganglia. Dr. Alpers' comments are well taken. In general, air studies in these cases were made for two purposes: to establish the diagnosis of presenile dementia or, in 2 cases, to rule out cerebral tumor. I think that in the early stages of these conditions encephalography is valuable. Later, of course, in the case of a patient who is mute and vegetative there is no difficulty in making the diagnosis, but earlier one can be of value to the patient and his family in making a prognosis if one is able to demonstrate an appreciable degree of ventricular dilatation without displacement.

Intramedullary Granuloma of the Spinal Cord: A Clinicopathologic Study.

Dr. Mary M. Larney (by invitation).

Of tumors within the spinal canal, the intramedullary group comprises about 15 per cent, and of these the granulomatous lesions are uncommon. The latter are usually tuberculomas or gummas, although a few cases have been reported in which no definite diagnosis could be made either by gross or by histologic examination. The total number in the literature to date is about 95.

The clinical picture in cases of intramedullary granuloma of the cord is that produced by an intramedullary lesion at any level, namely, one of compression and destruction of the cord, with no discrimination as to age or sex. Except in rare instances, tuberculomas of the cord are hematogenous, occurring either as part of generalized tuberculosis or from dissemination of a pulmonary lesion. In some cases the tuberculous focus may produce no clinical symptoms, and in a few instances there may be no evidence of tuberculosis elsewhere. The changes in the spinal fluid are nonspecific except in cases in which the lesion is associated with tuberculous meningitis.

Gumma of the spinal cord is a late development of syphilis, representing part of a more widespread involvement, and originates in the meninges with extension into the cord substance. The Wassermann reaction of the spinal fluid may or may not be positive, and final diagnosis often rests on evidence of the disease elsewhere.

Six cases from Philadelphia General Hospital of intramedullary granuloma of the cord in patients of ages ranging from 23 to 65 years are presented. In 5 of these cases the chief signs and symptoms on admission to the hospital were those of transverse myelitis or a neoplasm of the cord, namely, weakness, paresthesias and decreased sensation in the lower extremities, reflex changes and incontinence, with rapidly progressive deterioration and death. In the sixth case there was clinical evidence of advanced pulmonary tuberculosis. In 4 of the cases a definite postmortem diagnosis of tuberculoma was made on the basis of the histologic appearance of the lesion and the presence of tuberculosis elsewhere, but in only 2 of these cases was there clinical evidence of extraneural tuberculosis on the patient's admission. In a fifth case, a tentative diagnosis of tuberculosis was made in the absence of any evidence of syphilis, and in the sixth no definite diagnosis could be made. In 4 of the cases studies of the spinal fluid were made, and in 2 the colloidal gold curves were abnormal. In 1 case a Froin syndrome was present. Otherwise, the changes in the spinal fluid were nonspecific. The histologic picture in all the cases was that of a chronic granuloma with central caseation and fibrosis, surrounded by lymphocytes and giant cells.

DISCUSSION

DR. HELENA RIGGS: The cases which Dr. Larney reported are of interest in that the possibility of tuberculosis of the central nervous system was not suspected, since the symptoms of tuberculosis elsewhere were few except in the last case. The other point of interest is the age of the lesion as compared with the duration of symptoms. Microscopic examination revealed a dense reticulum in all cases, suggesting that, as Hassin stated, the neurologic signs are the result of the reactive process rather than of the tuberculosis itself. In other words, there is a tuberculous focus in the cord to which the nervous system reacts as to a foreign body by laying down connective tissue, so that gradually the substance of the cord is affected as a result of alteration in circulation produced by the scar tissue.

DR. CHARLES RUPP: As Dr. Larney has shown, the clinical diagnosis of these cases is difficult. There is nothing specific about the neurologic picture, and evidence of tuberculosis elsewhere in the body is often absent. In some cases, even at autopsy, no extraneural tuberculous focus can be seen. Possibly it existed in these cases, but if so, it was not detected. I should like to ask Dr. Larney whether the spinal fluid findings were of any value in the clinical diagnosis.

DR. FRANCIS C. GRANT: I shall speak of another type of granuloma of the spinal cord.

When I saw the title of Dr. Larney's paper, I recalled a similar case in my experience. I have a colored photograph of the operative field, showing the appearance of such a lesion. The case was that of a boy of 17 years of age, who three weeks prior to his admission to the University Hospital had been struck from behind by a barrel. He did not think much about it, but four or five days later he noticed numbness and within a week had pronounced paralysis and weakness of the extremities and difficulty of sphincter control. He was finally brought to the neurosurgical service, where operation was performed. An abscess of the spinal cord was encountered. This boy did not recover after the operation and eventually was taken home by his parents. I saw him eighteen months later, when he was still completely paralytic. Culture of the purulent material from the abscess taken at the time it was exposed revealed nothing, and I suspect that the boy had a granulomatous abscess. He had no pain. In most cases of such abscesses, in my own experience, onset has been with pain in the lumbar region. It is just another type of granuloma, and I agree with Dr. Larney and Dr. Riggs that the cause of the paraplegia is pressure on the cord.

DR. SAMUEL B. HADDEN: I should like to ask whether there was a sudden onset of the neurologic symptoms in any of these cases. Several years ago, in my service at the Philadelphia General Hospital, I had a case, that of a boy, in which symptoms of cerebellar disorder developed suddenly. Necropsy showed an old tuberculoma in the cerebellum. The sudden development of symptoms presumably was the result of a suddenly induced vascular disturbance. Was a similar symptom complex noted in any of these cases?

DR. MARY LARNEY: In 1 case the diagnosis was doubtful. The Wassermann reaction of the spinal fluid was negative and that of the blood positive, with a history of treatment, and in the literature the consensus is that the Wassermann reaction of the spinal fluid may or may not be positive.

Dr. Grant's case was interesting, especially since most authors seem to think that when the lesion is single and discovered early surgical removal often gives complete recovery.

Neurinoma of the Twelfth Cranial Nerve. Dr. Michael Scott and Dr. Henry T. Wycis.

Neurinoma of the twelfth cranial nerve is rare. Hass (*J. Neuropath. & Exper. Neurol.* **5**:66, 1946), in a review of the literature, found only 4 cases—2 of extracranial and 2 of intracranial lesions—and he reported 2 cases of intracranial neurinoma of his own.

The authors presented the following case: A white woman aged 50 complained of headaches, vomiting, staggering, hoarseness, numbness and weakness of the right hand over a period of three months. The headaches had been present for almost two years. In addition, she observed that when she ate candy, but not other sweetened foods, she promptly choked and had to have some one slap her on the back. She insisted that this reaction occurred only when the sweet sensation reached the back of her throat, and that she did not have it to sour or salty foods. She did not remember her reaction to bitter foods.

The past history was irrelevant. Neurologic examination showed slight blurring of the margins of the disks; a slight decrease in pain, temperature and light touch sensibility over the first division of the right trigeminal nerve; weakness of the right side of the soft palate, with absence of the gag reflex of this side, and paralysis of the right vocal cord. The right trapezius muscle was slightly atrophied, and the tongue was completely paralyzed on the right side, with marked atrophy and fibrillations on this side. Hoffmann and Oppenheim signs were present bilaterally. There was no Babinski or Chaddock sign. There was slight weakness in the grip of the right hand. Pronounced dysmetria was present on the right, with a slight bilateral intention tremor, which was more conspicuous on the right.

The provisional diagnosis was extramedullary tumor compressing the right ventrolateral surface of the medulla.

The laboratory studies revealed nothing abnormal. Routine stereoscopic roentgenograms of the skull were reported as normal.

A high cervical laminectomy and suboccipital craniectomy, done on July 31, 1945, revealed a tumor the size of a walnut compressing the right side of the medulla. It was encapsulated and had multiple nubbins. One extended mesiad, against the medulla; another, caudad, partly compressing the vertebral artery, and another, cephalad, compressing the posterior surface of the cerebellum. The ninth, tenth, eleventh and twelfth cranial nerves were enmeshed in the tumor. The lesion was connected by a broad base to the jugular foramen and the hypoglossal canal (anterior condyloid, foramen). The base of the tumor was resected and coagulated and the tumor delivered. No bone was removed from the anterior condyloid or the jugular foramen. After the removal of the tumor, the proximal portions of the ninth, tenth and eleventh cranial nerves were seen, but there was no evidence of any part of the twelfth cranial nerve, which apparently had been completely enmeshed in the tumor.

Special right and left posterior oblique views of the skull after operation revealed a defect measuring 2 cm. in diameter, involving the hypoglossal and the jugular foramen on the right side.

The microscopic diagnosis was neurinoma.

Examination one and one-half years later showed no change in the preoperative paralysis of the cranial nerves. The patient has been working regularly and has no complaints.

DISCUSSION

Dr. Henry Wycis: Dr. Scott and I were led to believe that the tumor arose from the twelfth cranial nerve, for two reasons: 1. Symptoms of hoarseness made

their appearance just before admission, whereas the atrophy of the tongue was far advanced at the time of admission and probably indicated long-standing involvement. 2. The ninth, tenth and eleventh cranial nerves could be visualized in the wall of the tumor, whereas at no time could the twelfth cranial nerve be seen.

DR. HENRY A. SHENKIN: I wonder whether the patient's vocal cords are functioning at present.

DR. MICHAEL SCOTT: The patient can now talk well. Before operation we had checked the vocal cords and found that they were paralyzed on the right side. They have not been examined since.

About seven years ago I presented before this society the case of a boy with a huge osteoma involving the right side of the base of the skull. Although he had complete paralysis of all the cranial nerves on the right side, he could talk well and could sing the scale perfectly. This case taught me how impossible it is to diagnose paralysis of a vocal cord simply by the sound or the strength of the voice. I always ask for a laryngeal examination.

Regular Meeting, March 28, 1947

Choreoathetotic Syndrome Following Fracture, with Bilateral Selective Softening of Globus Pallidus (Probable Fat Embolism). DR. ALEXANDER SILVERSTEIN.

The following case is of particular interest because the long survival period of five months permits the recording of a most unusual clinicopathologic syndrome following trauma which is often overlooked and is of particular interest in the field of neurology.

REPORT OF A CASE

On June 11, 1945, M. E., a 65 year old woman, was brought into Temple University Hospital with a history of having been forcibly thrown to the floor of a trolley car that had come to a sudden stop. Other than the local findings, and roentgen disclosures of fracture, the examination, including laboratory studies, gave negative results.

Course.—Shortly after admission to the hospital, Buck's extension was applied, and the patient appeared to be getting along fairly well until June 17, when the nurse observed that on occasions she would act "funny"; that is, she would suddenly sit up in bed and appear bewildered, while at other times she would remain unusually quiet.

On June 18, under light "avertin" (tribromoethanol solution U. S. P.) and nitrous oxide anesthesia, the fracture was exposed and a Thornton plate applied. The entire operative procedure lasted fifty-five minutes. The patient's condition before, during and after the operation was considered good. The blood pressure at the beginning of the operation was 140 systolic and 90 diastolic; at its completion it was 160 systolic and 80 diastolic.

When the patient was returned to the ward she continued to remain somnolent and later became restless, delirious and incontinent. The temperature was elevated to 101 F., the pulse rate was 100 and respirations were 24. The next day twitchings and choreiform movements of the muscles in all the extremities became so pronounced that restraints were necessary. After two days there developed severe choreoathetoid, jerking movements of all the extremities. There were frowning, pursing of the lips, bizarre facial grimaces and twisting and rolling movements of the tongue. Speech was explosive, dysarthric and almost unintelligible. All

the extremities were in constant motion. The legs were thrown about and the head jerked. In addition to the sudden, patternless, choreic movements in the arms and legs, there were slow, twisting athetoid movements of the hands and feet. Also, for a period of three weeks there was a tendency toward a ballismic pattern in the movements. The hyperkinetic manifestations would disappear during sleep or after inducing sleep with hyoscine scopolamine hydrobromide. The mental picture of confusion, disorientation, hallucinations and loss of memory indicated an organic type of psychotic reaction. Except for a short period of fourteen days during which there appeared to be an improvement in the mental picture, in that the patient was able to answer questions and carry out simple commands, the condition remained unchanged until she died six weeks later.

Pathologic examination made by Dr. B. J. Alpers and associates is reported as follows: "Gross Specimen: The meninges are moderately thickened over the convexity of the hemispheres. The gyri on the inferior surface of the left temporal lobe toward the anterior tip show sufficient atrophy so that the intervening sulcus spreads almost to a distance of 1 cm. This atrophy extends for about 5 cm. in length. Coronal sections stained with myelin reveal a dilatation of the ventricular system and flattening of the ventricular surface of the caudate nucleus. The striking feature is a selective, bilateral demyelination of the globus pallidus in both medial and lateral segments. In the substantia nigra there is also a similar, bilateral demyelination running parallel to the pes pedunculi.

"Microscopically, the areas of demyelination show extensive loss of tissue, gitter cell formation and mild gliosis at the edge. The red nuclei show a paucity of cells and those present are pale and distorted. Sections through the temporal cortex show marked atrophy of the cortex with thinning of the gray matter, neuronal loss and a helter-skelter arrangement of the remaining neurons so that laminations are not sharply defined. The arterioles are somewhat thickned and hyalinized, and there is pseudocalcification of the arteries.

"With sections stained for fat there are small collections of fatty material in some of the arterioles of the cortex; these collections appear chiefly as homogenous masses in the lumen of the vessels. However, oval-shaped masses are also present. Near the area of softening in the pallidum is seen a collection of fat about one of the arterioles. Large amounts of fat are also present in the phagocytes as well as in the ganglion cells themselves."

The diagnostic report from Dr. Alpers' laboratory was "cerebral infarction, probably fat embolism."

Comment.—Although the histopathologic picture in this case cannot be said to be typical of fat embolism, lacking as it does the characteristic features as observed in acute cases, there is sufficient evidence to warrant such a consideration. In the first place, fat embolism is relatively common in cases of intertrochanteric fractures of the femur occurring in elderly persons. Often the manipulation of the fracture under an anesthetic has been known to result in this complication. Secondly, in this case there was some evidence that the pathologic process had been present in a mild degree prior to the operation as characterized by the temporary periods of mental changes, and lastly, the striking feature of the bilateral selective softening of the globus pallidus in our case—a change usually found in carbon monoxide poisoning—has also been described as a special feature in a case of cerebral fat embolism reported by A. Meyer. His patient, a child, died following a bomb explosion. Here, too, the question of carbon monoxide poisoning came up for discussion, and subsequently was excluded.

One of the chief objections to the diagnosis of fat embolism in this case is the factor of anesthesia, since the patient continued to remain somnolent following

the operation. Although this sequence has been stressed as characteristic of the postanesthetic syndrome, there are many instances of proved cases of fat embolism of the brain wherein the patient never reacted from the anesthetic, and were it not for special studies with specific fat stains, the condition could have been labeled as postanesthetic fatality. An excellent example of this is reported by Cammermeyer (*Acta psychiat. et neurol.* **12**:33, 1937).

Courville, who has written most extensively on these postanesthetic cerebral disturbances, finds it difficult to account for all the recurrent episodes which so often appear in patients who survive for an interval of days or weeks following the anesthesia. Nor is it possible to explain the progressive mental failure, after an interval of apparent recovery, in these cases.

In the present case, the patient received a "mild 'avertin'-nitrous oxide anesthesia," with no cyanosis and no respiratory disturbance. Granting that a mild degree of asphyxia was present which escaped the attention of the anesthetist, it is most unlikely that this could account for the extensive damage to the brain.

In order to understand the factor of fat embolism in this case, one must accept the mechanism of production of fat embolism by alteration of the chemical composition of the blood, in which the normal emulsified fat in the blood is changed to globules of embolic fat under certain conditions such as trauma, strong alkalis, sickle cell anemia and poisons (carbon monoxide, chloroform, phosphorus).

A discussion of fat embolism will not be attempted at this time. A voluminous literature deals with every phase of the problem from the experimental to the medicolegal aspects.

It is of special interest in the field of neurology because of its role in trauma to the head, electroconvulsive therapy, "blast injury" and neurologic complications folowing surgical procedures, labor, as well as minor operative maneuvers such as orthopedic manipulation. The medicolegal implications are of particular interest since fat embolism may play some role in the post-traumatic syndromes, not only in cases of cranial trauma but also in extracranial injuries. The clinical picture is well established and in the typical case readily diagnosed. The "free interval" (absent in trauma to the head and anesthesia) followed by a sudden onset of pyrexia, rapid pulse, dyspnea and various neurologic symptoms and signs (convulsions, delirium, paralyses, decerebrate rigidity) is a characteristic sequence of events. Cutaneous petechiae and embolic changes in the retina have been considered of pathognomonic significance when taken into account with the rest of the clinical picture. Laboratory tests for lipemia, lipuria, fat in the sputum and roentgen examination of the lungs all help to establish a diagnosis.

DISCUSSION

DR. FRANCIS M. FORSTER: In opening the discussion on the interesting case which Dr. Silverstein has just presented, I should like to limit myself to discussing two particular points of this problem. The first one deals with the lesions, and I am particularly interested in the fact that these were symmetric lesions. I should like to point out that essentially they were bilateral lesions involving the medial and lateral segments of both globus pallidi and symmetric lesions of the most ventral portion of both substantiae nigrae. Nonsymmetric lesions also occurred, notably the one in the caudate nucleus. The symmetric lesions bring up a troublesome point when one considers the blood supply of these symmetrically involved areas. The medial segments of the globus pallidus receive their blood supply from the anterior choroidal artery, while the lateral segment, in about one quarter of the cases according to L. Alexander (Vascular Supply of Strio-Pallidum, *A. Re-*

search Nerv. & Ment. Dis., Proc. [1940] **21**:77-132, 1942), is also supplied by the anterior choroidal artery, in another quarter by one or more of the striate arterioles of the middle cerebral artery, and in the remaining one half of the cases by both the anterior choroidal and the middle cerebral striate arterioles.

This would give a three to one possibility of a double supply for the medial and lateral segments and adding up the two sides would involve four arteries. As far as the substantia nigra is concerned, the blood supply of this area is received from paramedial branches of the arteries of the interpeduncular fossae, and this again would add two more vessels. One point which I think is vexing in this case is that there must be probably at least six vessels producing such symmetric lesions, which makes it a little difficult to visualize embolic phenomena picking out so neatly the bilateral vessels.

There is some variation in the age of the lesions. The lesion in the caudate nucleus was somewhat older and had less gitter cell formations and more gliosis than did the other lesions, which were approximately of equal chronologic age. However, I think Dr. Silverstein points out that there may be subsequent showers of emboli and that might very well explain age variations.

As far as symmetric lesions are concerned, Alexander in his paper in the research publications on basal ganglia described a patient with bilateral symmetric lesions of the substantia nigra, and these arose on the basis of endocarditic emboli so that there is some evidence in favor of Dr. Silverstein's premise that these lesions are embolic in nature; in Alexander's case there were not as many lesions nor were they as beautifully symmetric. If these lesions are embolic, of course, there is always that question which is hurled at the man who presents lesions as embolic as to how the emboli passed through the lung, and I wonder if Dr. Silverstein would have any notes on that in this particular instance. If those were emboli filtrating into these larger branches of the anterior choroidal artery, the emboli must have been appreciable in size and it is a little difficult to see how they could have passed through the pulmonary capillary bed; so I wish Dr. Silverstein would elucidate this.

The second point which I would like to discuss, and this time perhaps come to Dr. Silverstein's aid, is the genesis of the symptomatology in an attempt to reconcile the clinical picture which his patient shows with the lesion shown at autopsy. This, as we are all aware, is often a very unsatisfying situation in dealing with lesions of the basal ganglia and one need only thumb through the reports of that same research meeting on the basal ganglia to find ample moaning about difficulty of reconciling lesions with clinical symtomatology. There seems, however, in this case tonight to be two distinct possibilities. First of all, the lesions I might say are those which most of us would expect to produce parkinsonism. Dr. F. N. Lewy, however, has stated that after two dozen cases of parkinsonism he was sure where the lesions ought to be. After the seventh dozen he was not quite so sure any more. But I think that even with some temerity one might say that in this particular patient some parkinsonian features might have been expected. However, they were not present and the picture described clinically was one of hemiballismus. We have come to consider hemiballismus as a sign of a lesion of the subthalamic body. There is, however, if one looks carefully, only a single case of a lesion of the subthalamic body only producing hemiballismus. In most of the cases there are lesions of more than the subthalamic body. In a recent report, Glees (*Brain* **69**:195, 1946) has worked out the anatomic connections of the subthalmic body, and it is rather interesting to note that the afferent fibers are from the medial and lateral segments of the globus pallidus and from the substantia nigra, and the chief efferent fibers project to the segments of the globus

pallidus, with some other connections presumably to the red nucleus. Now if that is so in this case, it would seem as though the subthalamic body was virtually isolated by having lost its chief afferent and most of its efferent connections. It is hard to see how the small lesion in the caudate nucleus could be invoked to explain the choreoathetosis because it was too small a lesion to be an extensive interruption of the supressor cortico-caudato-thalamo-cortical circuit, which is largely indicated for the lesions in athetosis.

There is a third possibility for the genesis of the lesions, and that is the peculiar psychomotor parakinetic activity originally described by Timme. This activity was also present in the case of Alexander's, that I previously mentioned with bilateral lesions of the substantia nigra, in which parkinsonism did not develop, but in which immediately after receiving the lesion the patient had a peculiar psychomoter activity with extreme uncontrolled movements, which have acquired the name of psychomotor parakinetic movements.

Dr. N. W. Winkelman: This is an interesting case from many angles. The anatomic angle has already been covered by Dr. Forster. From the clinical side, there are also some interesting features, and Dr. Silverstein has mentioned one of them which he skipped over hastily and which deserves, I believe, a little further consideration. This is the question of the influence of anesthesia: It is well known that anesthesia alone can without trauma send a shower of fat globules into the brain. It has been found that if a patient is anesthetized after a fatty meal, there is a greater danger of provoking fat embolism than if the patient is starved prior to operation. That is, theoretically, at least, one of the reasons for "preparing" a patient for operation. At one time it was thought that the giving of chloroform might even prevent fat embolism. As a matter of fact, experimentally it produced rather than prevented it. The giving of an anesthetic in this case is, therefore, not against the diagnosis of fat embolism.

There are certain things in the clinical study that might have been taken into account. Knowing as I do, Dr. Silverstein's interest in fat embolism, I wonder if during the lifetime of the patient he was privileged to make further studies of that patient, performing the test for fat in the saliva (Warthin's sign), which is supposedly diagnostic, and the test for fat in the urine (lipuria).

One of the factors against the diagnosis of fat embolism is the long duration of the illness. Most patients with fat embolism die fairly quickly. The symptoms come on quickly. There may be a free interval, and then a rapid and progressive and irreversible course to death. That whole picture has been divided into three different components: renal, pulmonary and cerebral. The three pictures may be combined into one.

There was fat in the blood vessels, but in small amounts. I had the opportunity of studying the section through Dr. Silverstein's courtesy. I would take issue with Dr. Silverstein on one point, and that is about the examination of the other organs of the body in cases of suspected fat embolism. In a series of unselected postmortem studies, in which fat embolism did not come into consideration, one investigator found over 50 per cent of the lungs of his patients had fat in the blood vessels, irrespective of the terminal disease. The conclusion has been reached that the presence of fat in the vessels of the lungs themselves—and that is one of the safety valves apparently—is not diagnostic of fat embolism. Fat in the blood vessels of the brain, however, is a different story. We do not ordinarily meet with fat in any great amount in the blood vessels of the brain.

It is plausible that in this woman the fat was slowly and definitely excreted by the kidney and by the lung, perhaps in the saliva, so that there was only a small amount of fat left after a period of five months.

The bilateral softenings were stressed by Dr. Silverstein. The pathologic picture as seen here I think would have been diagnosed carbon monoxide poisoning without the benefit of the history. It is extremely interesting that he has uncovered a similar case in the literature.

DR. GEORGE D. GAMMON: I should like to ask Dr. Forster one question. I understood him to say that the connection between area 4S and the caudate nucleus might be accountable for the symptoms here. I was not aware that there was any anatomic pathway between 4S and the caudate nucleus. If there is, did you see any degeneration in that pathway, and will you tell us what it is?

DR. FRANCIS M. FORSTER: I think I can answer that by saying that I said I did not think the symptoms could be attributed to a lesion of the area 4S-caudate nucleus- thalamocortical circuit in this case. I am sure we are all well aware of the discovery of this circuit by Dusser deBarrene and McCullough. Area 4S exists in man and has been shown by Bucy and Garol to be a real suppressor area. The anatomic pathways of the circuit are not completely known, but perhaps the physiologist is a jump ahead of the morphologist this time. I want to make clear, Dr. Gammon, that I said that in this case I did not believe that this circuit was involved because the lesion of the caudate nucleus was a very small one.

DR. ALEXANDER SILVERSTEIN: My first case of cerebral fat embolism presented a characteristic clinical and pathologic picture and yet remained undiagnosed for a long time until Dr. E. Spiegel carried out special studies and proved the diagnosis. Clinically, the case was a mystery to the various consultants, and even after careful histopathologic studies (without the use of fat stains) the true condition was unsuspected and such diagnoses as cerebritis, endarteritis, hemorrhagic encephalitis and cerebral purpura were made to explain the clinical finding.

Dr. Forster finds it difficult to interpret the symmetric pattern of the lesions in the basal ganglia on the basis of arterial distribution. I am unable to shed any light on this except to state that other factors such as venous occlusion and atypical vascular patterns may play a role. Be that as it may, this peculiar selective softening in the globus pallidus in cerebral fat embolism of the brain is not an isolated instance, as was reported recently by Meyer in a child who died following a bomb explosion (*Proc. Roy. Soc. Med.* **34**:651, 1941).

Dr. Forster asked the question as to how the fat gains entrance into the systemic circulation. This phase of the problem has been extensively treated in the literature. In addition to the usual mechanism of the absorption of free fat at the site of a fracture into the venous circulation, right side of the heart, pulmonary vessels, and through the small capillaries, into the systemic circulation, there is interesting experimental work to prove that the blood plasma itself under certain conditions may be the source of fat. That is, the absorption of free fat and the products of protein decomposition into the blood stream may result in physiochemical alteration of the normal emulsified fat into globules of fat sufficient to produce anoxemic foci. It would seem that this mechanism would help to explain the severe and fatal cases of fat embolism which result from relatively minor injuries as well as those cases of nontraumatic origin.

Dr. Winkelman was kind enough to elaborate on the various features of fat embolism which I did not do, chiefly because of lack of time. His question as to why special studies for fat were not carried out in my case can be answered simply by stating that the complication of fat embolism was not considered in the clinical picture until more than three weeks after onset, as which time it was too late to conduct such studies.

Dr. Winkelman's statement that the long survival period in this case is a point against the diagnosis of fat embolism is well taken, since it is true there is no report in the literature of a similar case. However, I do not see why a disease which causes such a serious pathologic process in the brain cannot also produce various forms of clinical pictures depending on the severity of the lesions in the brain.

My emphasis on the importance of the examination of the various viscera in cases of fat embolism is not my own curious idea but rather a fact emphasized by various observers. That is, the typical pathologic lesions in the brain may be present and yet the fat globules in the vessels of the brain may be absent. Instead, the fat may be concentrated in one of the viscera, such as the kidneys, lungs and liver.

I wish to express my thanks to Drs. Forster, Winkelman and Spiegel for their discussion as well as their great help in the study of this case.

STUDIES IN CEREBRAL CONCUSSION

A. Changes of Convulsive Reactivity. Dr. M. Marks (by invitation).

A study was made of the effect of concussion on the convulsive reactivity and associated disturbances to ascertain some of the mechanisms on which changes of convulsive reactivity depend. Immediately following a concussive blow, convulsions produced by the injection of "metrazol" in rats ceased for thirty to sixty seconds. After a pause, single contractions or groups of contractions appeared and the frequency of the convulsions was reduced in the first few minutes following the blow.

To measure the convulsive reactivity for more prolonged periods following the trauma, electrical stimulation with the skull intact was utilized. In the majority of the animals (rats and cats) the concussion was followed by an increase of threshold; in some cases this was demonstrable in a few minutes, in others not until the passage of several hours. In many cases the increase of threshold lasted several weeks, at a time when the general behavior and reflexes seemed normal. There was no strict parallelism between the intensity of concussion and the changes of convulsive reactivity. In a small part of the animals with concussion there was a decrease of the convulsive threshold. It has been impossible to explain these changes by studies of cerebral metabolism, e.g., of oxygen uptake. Electrical determinations of cellular membrane density (polarization index, Spiegel, Henny, Wycis and Spiegel-Adolf), however, yielded interesting results. There was a decrease of membrane density of more than 20 per cent associated with concussion, usually most marked within thirty to sixty minutes, after which time there was a slow rise in the value; however, four hours after the blow a definite decrease was still present. This change could not be produced in dead animals, and in control experiments it was shown not to be related to transient disturbances of cerebral oxygen supply associated with the postconcussive apnea.

The possibility was considered that acetylcholine released from injured cells was responsible for the changes of convulsive reactivity. However, since "metrazol" convulsions ceased following a blow to the head in atropinized rats just as in the animals which had not received atropine, it seems probable that the release of acetylcholine is not responsible for the depression of convulsive excitability. If the changes of convulsive reactivity were due to impairment of cellular surfaces alone, one should expect, in view of the decrease of density observed, that overexcitability would occur more frequently than we found. Furthermore, the increased convulsive threshold lasts much longer than the transitory disturbances of

cell membranes. We must look, therefore, for other, intracellular, factors to explain the changes in excitability. The existence of such factors (particularly interference with nucleic acid compounds) is indicated by one of the subsequent papers presented in this symposium.

B. The Mechanical Role of the Cerebrospinal Fluid in Cerebral Concussion. DR. HENRY T. WYCIS.

Because of certain conflicting views regarding the alleged role of the cerebrospinal fluid in trauma of the head, the author carried out a series of experiments on 9 dogs in which the threshold value of the concussive blow and the severity of cerebral concussion were compared before and after encephalography. The experiments showed that following withdrawal of cerebrospinal fluid and subsequent injection of air not only could concussion be produced with blows of less energy but also the severity of the concussion was increased. Two control dogs subjected to the same conditions, except that encephalography was omitted, failed to show any significant changes. The possibility could not be denied that with an intact cerebrospinal fluid system, the pressure of the fluid in the ventricular system is increased during concussion, thus causing injurious effects to the ventricular walls (Duret). However, these experiments seem to indicate that after replacement of cerebrospinal fluid by air the loss of the cushioning effect of the cerebrospinal fluid is more important than the absence of the injurious effect of increased intraventricular pressure. Therefore, there seems reason to assume that the cerebrospinal fluid in the subarachnoid space exerts a certain protective effect on the brain in trauma to the head.

C. Physicochemical Studies of the Cerebrospinal Fluid. DR. M. SPIEGEL-ADOLF (by invitation).

Ultraspectrophotometric measurements were made on 45 cerebrospinal fluids from patients who had sustained a cerebral concussion. The absorption in terms of extinction coefficients (E) was determined over a range of 3,100 to 2,200 angstroms. The cerebrospinal fluids of neurologically normal patients who had not received barbiturates, blood transfusions or roentgen radiation showed S-shaped absorption graphs or only slight selective absorption. At 2,650 angstroms the mean value of the extinction coefficient is 1.24 ± 0.59 (m_1). All cerebrospinal fluids of the patients in whom the interval between accident and lumbar puncture was below two months showed selective absorption with a maximum at about 2,650 angstroms. The mean of the extinction coefficient values was 2.47 ± 0.73 (m_2). The differences between m_2 and m_1 are statistically significant. In patients on whom lumbar puncture was repeatedly performed after the accident, selective absorption usually appeared after two hours, reached its maximum after four days and slowly decreased during the next weeks. It could be ascertained that neither proteins nor lipids are the cause of the selective absorption of the pathologic cerebrospinal fluids, which most probably is due to the presence of normally occurring ascorbic acid and of nucleic acids and/or their cleavage products containing purine and pyrimidine groups. The presence of the latter substances in the cerebrospinal fluids of patients with concussion may be correlated with experimental findings of Windle, Groat and Fox (chromatolysis following cerebral concussion). Since, according to Casperssen, Gersh and Bodian, the tigroid bodies contain nucleic acids, it may be inferred that the nucleic acids of the cerebrospinal fluid originate in the nerve cells and indicate chromatolysis.

Finally, evidence has been given that cerebrospinal fluids of patients with concussion contain enzyme-like substances which not only destroy the selective absorption of their own medium but also of added solutions of animal and plant nucleic acids, while normal spinal fluids are practically inactive. Enzymatic substances could also be found able to produce chromatolytic changes on anterior horn cells of cats' spinal cords in vitro. It seems, therefore, that contrary to the results of routine examination, both the spectrophotometric and enzyme studies demonstrate definite changes in the cerebrospinal fluids of patients after cerebral concussion. The importance of these findings for differential diagnostic purposes and medicolegal problems is obvious.

D. Physiopathologic Mechanisms with Special Reference to Midbrain and Hypothalamus. A. J. LEE, A.B. (by invitation) and DR. E. SPIEGEL.

A number of physiologic changes induced by cerebral concussion such as disturbance of consciousness, changes of body temperature and hyperglycemia suggest impairment of the hypothalamus, while loss of labyrinthine and body righting reflexes (Spiegel, E. A., and Spiegel-Adolf, M.: *Federation Proc.* 5-98, 1946) point to involvement of the tegmentum mesencephali. In order to ascertain whether these regions are affected in cerebral concussion, their electric discharges were recorded by means of needles implanted by the aid of a stereotaxic apparatus in the base of the skull. For a study of the electrical activity of the cerebral and cerebellar cortex, phonograph needles were inserted in the skull. Acceleration concussion was produced by blows applied to the head of the freely swinging animals (cats). Following concussive blows, the changes of the electrical activity of the hypothalamus, midbrain tegmentum and cerebellum (reduction of the amplitude or abolition of all electrical activity, appearance of slow waves, of groups of high amplitude waves) were quite similar to the electrical disturbances recorded from the cerebral cortex. In some cases the impairment of function as indicated by the electrogram was more marked in subcortical areas than in the cerebral cortex. Histopathologic studies revealed, in some instances, proliferation of the fiber glia around the third ventricle in the chronic stage after the cerebral trauma and subependymal edema around the aqueduct in the acute stage.

(This research was aided by a grant from the John and Mary H. Markle Foundation.)

DISCUSSION

DR. JOSEPH C. YASKIN: I am not going to discuss this at length for one good reason. I think Dr. Spiegel and some of the others know it. I do not believe I have the capacity to grasp the magnitude of this work in one hour, and it took exactly fifty-five minutes for all these papers to be read and presentations to be delivered. I do not think Dr. Spiegel expects anybody to comprehend this work on so brief a presentation.

However, there are some features that impressed themselves on me. If I had arranged this program I think I should have started with Dr. Spiegel's presentation. It is a little bit more concrete and more readily understood by us.

The presentations by Dr. Spiegel and by Dr. Marks give us some objective data on the pathophysiology of concussion which we heretofore never had. It is another step to the understanding of this troublesome problem.

Then the work by Dr. Spiegel-Adolf is also extremely important because it gives us a new light into the chemical changes heretofore completely missing. A spinal fluid estimation at any hospital simply tells us there is no blood, no increase in protein and cells, and that the results of all the other studies are nega-

tive from an organic standpoint. At times the history in the case is not clear and the diagnosis is often questioned. Nevertheless, patients with genuine cases of concussion have headache and dizziness, and exhibit irritability, etc., from weeks to months after the concussion, and therefore the studies suggested by Dr. Spiegel-Adolf may help in making a more accurate diagnosis.

I was not quite so clear on the work of Dr. Marks, and I am sure it is not his fault. I think I should study this in great detail before I can talk about it.

And, lastly, the work of Dr. Wycis was of great interest in that it touches on a great many old spots that need repetition for those of us who are busy examining patients all the time and are too long and too far away from the laboratory.

Dr. Robert A. Groff: I should like to ask one question concerning Dr. Wycis' work. How long after the encephalogram was done was the animal subjected to the injury? If the injury was inflicted within several hours after the injection of air, one must take into consideration the factor of shock induced by the insufflation of air.

Dr. Spiegel's presentation casts a new light on the definition of cerebral concussion. My conception was that it was a temporary cessation of cell action, and this was reversible. Does Dr. Spiegel want to comment on this impression in the light of his findings?

Dr. Henry T. Wycis: Regarding Dr. Groff's question, we did consider that it was necessary to allow these animals to recover from the shock of the encephalographic procedure before they were subjected to concussion a second time. Therefore we waited a period of twenty-four to forty-eight hours following withdrawal of fluid, at a time when the animals were up and about and had recovered from the shock of the procedure.

Dr. E. Spiegel: I want to thank the discussants for their kind remarks. Dr. Groff brought up a very important question regarding the concept of cerebral concussion. I do not want to change the basic concept of a transitory cessation of cerebral function, but we have to bear in mind that there may develop, at least in some instances, rather prolonged postconcussional symptoms. The periventricular changes we described in the diencephalon may perhaps indicate one of the pathologic mechanisms responsible for these subacute or chronic postconcussional symptoms. The primary goal of the papers we presented this evening was, however, to ascertain by physical and physicochemical methods the nature of the changes induced in the central nervous system in cerebral concussion. Unfortunately, the old concept of "molecular" changes still survives in the recent literature, even in Denny-Brown's papers on this subject. My old teacher, Obersteiner, emphasized as early as in the beginning of this century that the concept of molecular changes should be replaced by chemical and particularly colloidochemical data. To supply such data is the main purpose of the work in which our group is engaged.

CHICAGO NEUROLOGICAL SOCIETY

Joseph A. Luhan, M.D., *Vice President, Presiding*
Regular Meeting, April 8, 1947

Hemiballismus: Report of Two Cases. Dr. Joseph A. Luhan.

Case 1.—W. T., a Negro aged 87, showed purposeless, flinging, throwing and thrashing movements of the left extremities, of four days' duration. These ceased during sleep. He complained of pain in the bruised and excoriated extremi-

ties and said that he was very tired. Examination showed no pathologic reflexes; the abdominal responses were preserved. The blood pressure was 162 systolic and 84 diastolic. Three days after admission he became confused, then delirious, and died the next day (eight days after onset), of bronchopneumonia.

The brain showed moderate cerebral arteriosclerosis and discrete, almond-shaped hemorrhage, 4 by 11 mm., occupying the general region of the right subthalamic body. Sections stained by the Weil method showed the extent of the hemorrhage. (4 slides)

CASE 2.—J. H., a white man aged 73, complained on admission of uncontrollable, violent thrashing movements of the left arm and leg, of one day's duration; the movements came on suddenly, appearing first in the leg. He knew that his blood pressure had been high for three years. On his admission it was 180 systolic and 110 diastolic. Examination showed continuous, violent jerking movements of the left arm and leg. The deep reflexes were difficult to elicit on the left side; the plantar responses were normal; the abdominal reflexes were absent. The movements ceased or diminished during sound sleep, became increased on attempts at voluntary movements and were uninfluenced by scopolamine or barbiturates in less than narcotic doses. The left extremities became bruised and excoriated in spite of protective padding.

Five days after his admission fever appeared, then parotitis and, finally, coarse rales in the lungs; he died about ten days after onset of the hemiballismus.

In addition to considerable atherosclerotic change, the brain revealed a discrete, almond-shaped hemorrhage, measuring 3 by 11 mm., at its maximum development in coronal section in the general region of the right subthalamic nucleus. The caudalmost extremity of the hemorrhage, measuring 1 by 2 mm., was seen at the coronal level of the external geniculate body, in the tegmental portion of the mesencephalon. (Slides) Probably in no other location can a cerebral lesion so small and so discrete produce a clinical neurologic disturbance of comparable violence.

Dr. Bucy has theorized that the suppressor circuit which is interupted, causing hemiballismus, runs from area 4-S into the caudate nucleus, the globus pallidus and the body of Luys, the return connections with the thalamus and the precentral region being unknown.

Postherpetic Argyll Robertson Pupil. DR. JOSEPH A. LUHAN.

T. B., a Negro woman aged 41, has multiple sclerosis. Thirteen years prior to this report she became paralyzed from the waist down; after a month or so she was able to walk again. Nine years before admission she had Bell's palsy, presumably of rheumatic origin, on the right side. Since then she has had exacerbations and remissions of weakness and numbness in the lower extremities. A laminectomy (from the fifth to the eighth thoracic vertebra) was performed at another neurologic facility in 1938. She has spastic paraparesis, with sphincteric weakness and neurogenic bladder. In 1944 she had herpes zoster ophthalmicus on the left side. Two years ago she was given an injection of alcohol into the left supraorbital nerve. The left pupil is small and fixed to light and contracts in accommodation; scars of ophthalmic zoster are present.

Lead Encephaloamyotrophy. DR. A. J. ARIEFF and DR. M. A. SCHILLER.

R. I., aged 45, a house painter, was admitted to Cook County Hospital on Dec. 24, 1945, because he was paralyzed and mentally confused. He had been

well until September 1936, when there developed jacksonian attacks, involving the left upper and lower extremities, without loss of consciousness. The attacks occurred once every two or three weeks and by April 1936 had increased in frequency to once a week. There was no aura, and the attacks lasted only a few seconds, without incontinence. In January 1936, one attack was said to have lasted five minutes, during which he lost consciousness. Preceding this attack he felt "as though his heart was coming out." At the time of onset he also had dull, aching pain in the left arm, occurring from two to three times daily to two to three times weekly and lasting from a few minutes to several hours.

The family history was essentially noncontributory.

In April 1936 he was seen by a neurosurgeon, who found the left palpebral fissure larger, the right platysma muscle stronger and the abdominal reflexes more sluggish on the left. The deep reflexes were equal on the two sides, and there were no pathologic reflexes. A roentgenogram of the skull was normal. The tentative diagnosis was intracranial tumor. On April 15, 1936, an osteoplastic flap was turned down on the right side, and arachnoiditis was observed.

The convulsions ceased, and the patient returned to his occpuation as house painter, in which he continued three years longer; he then left this work because he began to fear falling. In 1942 he had onset of attacks, characterized by paralysis lasting from several seconds to one or two minues, with spasticity of the extremities; these attacks occurred every three to six months for two years. He was then free of spells for eight months. In October 1945 he became slow in his movements and dragged both feet. Six weeks prior to admission, on attempting to arise from a chair, he fell, without loss of consciousness, and became paralyzed, completely bedridden and incontinent. Mentally, he changed from a cheerful, talkative person to a quiet, inattentive, depressed man, and before admission he was confused and out of contact.

Physical examination in December 1945 showed nothing of significance. A surgical scar was present over the right temporofrontal region, and a large decubitus sore, over the sacrum. No lead line was noted on the gums.

Neurologic examination showed pronounced atrophy of the legs and thighs, involving mainly the quadriceps muscle, and moderate atrophy of both upper extremities, including the interosseous muscles. The hand grip was feeble, especially on the left. There was pronounced bilateral paresis of the lower extremities with contracture of both feet in plantar flexion. The knee and ankle jerks were better on the left side than on the right; no pathologic reflexes were found. There were rhythmic movement of the toes, foot, thigh and hand on the left side and anesthesia along the dorsum of the right foot in the distribution of the peroneal nerve. The deep reflexes of the upper extremity were somewhat better on the right side than on the left. In spite of the paresis, there was spasticity of the lower extremities, more intense on the left. The right side of the face contracted better than the left; the tongue protruded in the midline, and its tip was smooth. The pupils were round and equal and reacted normally to light. There was a 4 D. elevation on both disks, with small hemorrhages about them.

Mentally, the patient was out of contact, apathetic and inattentive. Examination of the spinal fluid revealed that it was normal, with a pressure of 330 to 360 mm. of water, and there was no block. The Wassermann and Kahn tests gave negative reactions; the total protein was 40 mg. per hundred cubic centimeters. Although the skin was ashen gray, there was no anemia or basophilic stippling of the red blood cells. The urine was normal. Roentgenograms of the bones revealed nothing unusual. The visual fields were normal.

The toxicologist's report showed 0.035 mg. of lead per liter in the urine and 0.069 mg. of lead per hundred cubic centimeters in the blood. The electroencephalogram showed strong 11 to 12 per second activity, no seizure discharge or build-up with hyperventilation and moderate asymmetry, with the whole left hemisphere showing less amplitude. While in the hospital, on June 10, 1946, the patient had a mild convulsion and was placed under treatment with phenobarbital, 1 grain (0.065 Gm.) three times a day. On Dec. 13, 1946, reexamination of the urine for lead revealed 0.10 mg. per liter, a definitely abnormal amount.

Examination at this time showed weakness of all extremities, particularly on the left, the hand grip and extensor muscles of the foot being especially involved. The deep reflexes were all brisk and equal on the two sides; ankle clonus was present bilaterally. There were no pathologic reflexes except for a Hoffmann sign bilaterally The cremasteric reflexes were diminished bilaterally; the lower abdominal reflexes were absent on both sides, as were the reflexes in the right upper and lower extremities; no sensory disturbance was present. The left palpebral fissure was slightly wider than the right; internal strabismus was present on the right, but the extraocular movements were normal. The pupils were equal and reacted well to light and in accommodation. The facial movements were slightly better on the left than on the right, and the tongue protruded in the midline; the palate was normal. Papilledema was still present on both sides, being greater on the left. There was atrophy of the extremities, especially of the interosseus muscles bilaterally, the right gastrocnemius muscle, the extensors of both legs and the adductors of the left thigh. There was a slow, coarse tremor of the outstretched hands.

This case was one of lead poisoning involving the brain, spinal cord and peripheral nerves, with toxic amounts of lead in the urine, but without the usual signs of the lead line, basophilic stippling of red cells or lead colic.

Dural Abcess. Dr. A. J. Arieff and Dr. A. Brown.

A white woman aged 60 was admitted to Cook County Hospital on May 15, 1946, with the complaint of severe pain in the back and in the right shoulder and oliguria. The pain started one week before her admission as a dull ache in the middle of the back, localized over the renal area and radiating down the back to the labia and thighs, and occasionally to the right shoulder.

Her past history, as obtained from Michael Reese Hospital, showed that she was admitted there in August 1932, with pain in the back, radiating to both thighs, of three weeks' duration. Three weeks before admission she had had an infected great toe on the right foot, followed by lymphangitis; the infected foot responded to treatment. The left knee jerk was not elicited, and in a few days the right also disappeared. There was retention of urine, and pus was found. Twelve days after admission a spinal puncture revealed pus, a culture of which showed Staphylococcus albus; a furuncle developed at the site of the puncture. Laminectomy of the eleventh and twelfth thoracic and the first lumbar vertebrae disclosed a localized abscess on the roots of the cauda equina.

Physical examination at the time of her admission to Cook County Hospital revealed an essentially normal condition. On the third day transverse myelitis developed in the lumbar area, which went on to ascending myelitis, until the level reached the fourth thoracic segment. Repeated spinal taps yielded nothing of significance until the forty-fifth day, when, at the level of the twelfth thoracic vertebra, a tap produced frank yellow pus, from which Staph. albus was obtained on culture. During her stay in the hospital, she received a course of sul-

fadiazine treatments, and at the time of her death, on the fifty-second day, she was receiving penicillin.

Arsenical Polyneuritis. Dr. H. Garner.

A white man aged 40 was admitted to Cook County Hospital on March 7, 1947, with the complaint of numbness, tingling, weakness and "hot sensations" in the hands and legs, of four weeks' duration. Six weeks before admission he had taken 5 capsules of rat poison (56 per cent arsenic, 20 per cent barium carbonate). Almost immediately he became nauseated and vomited. Gastric symptoms continued for about four days before he sought medical attention. Within a week the skin of his face peeled, followed by exfoliative dermatitis of the entire body, with intense pruritis.

Physical examination revealed nothing significant; the liver was palpable 1 fingerbreadth below the right costal margin and was tender; the nails were brittle, and horizontal white lines were visible below the base of the nail. Neurologic examination revealed that the cranial nerves were normal. Examination of the peripheral nerves showed pronounced motor atrophy of the upper and lower extremities; tonus was decreased; extreme weakness was present in all extremities, being most noticeable at the periphery; the muscles were very tender, and fibrillary twitching was present in the deltoid area and in the muscles of the forearm. Sensory, postural and vibratory sensations were absent in the upper and lower extremities. Pain, touch and temperature sensations were spotty in all extremities, some areas being hypersthetic, while the neighboring area was hypersthenic. All deep reflexes in the extremities were absent. Abdominal and cremasteric reflexes were present; no plantar response could be obtained.

Results of laboratory tests, including spinal fluid studies, blood counts, serologic tests and urinalysis, were within normal limits. Repeated examinations of the urine, the hair and the nails for arsenic gave negative results.

For three successive days 200 mg. of BAL (2, 3-dimercaptopropanol) was given intramuscularly. No secretion of arsenic followed its administration.

The case is presented because of the relative infrequency of arsenical polyneuritis. The use of BAL is mentioned to call attention to the fact that when arsenic has become firmly fixed in the tissues it cannot be displaced through its administration.

Recurrent Subarachnoid Hemorrhages. Dr. Ernst Haase.

A white girl aged 24 was brought to Cook County Hospital on Jan. 30, 1947, after a sudden collapse, in a stuporous condition. Neurologic examination revealed nothing abnormal except for intense rigidity of the neck and back; the spinal fluid was bloody and under an initial pressure of 180 mm. There was no history of headache or vomiting or evidence of internal abnormalities. The blood pressure was 100 systolic and 80 diastolic. A diagnosis of subarachnoid bleeding due to congenital aneurysm was made.

On February 3 the spinal fluid was still bloody; on February 13 it was xanthochromic, with a pressure of 110 mm. Gradual clinical improvement followed.

On February 20 the patient got out of bed to smoke a cigaret and collapsed again. There were severe occipital headaches, rigidity of the neck, a Rossolimo sign on the left and diminished patellar reflexes. The spinal fluid was bloody, with a pressure of 193 mm. Again, gradual improvement took place, but after ten days she experienced a sudden, excruciating pain in the neck and right frontal

headache. She was restless and fell into a stupor. The patellar and achilles reflexes were absent; the left nasolabial fold appeared flattened, and the neck and back were very stiff. She remained in a lethargic state, was confused and seemed to be in great pain. On March 9 the temperature rose to 101 F.

Ligation of the right internal carotid artery was perfromed by Dr. Harold C. Voris. The operation was followed by uneventful recovery. At the time of this report, five weeks after the operation, the patient has only slight rigidty of the neck; the facial palsy has disappeared. The patellar and achilles reflexes have not returned.

Myotonic Dystrophy. Dr. I. C. Sherman and Dr. Eli Tigay.

A white man aged 44 gave the following history: About five years prior to his admission he noticed weakness of his arms; to date, this has become progressively worse. Soon thereafter he noted weakness in the legs and could not stand long. The legs were stiff when he arose in the morning, and on his walking about they loosened up. There were no pains, paresthesia or sphincter disturbances. He had had "eye trouble" since 1940. His family and occupational histories were without significance so far as his present condition was concerned. He stated he has been impotent for the last two years.

Neurologic examination showed a negative Romberg sign; bilateral foot drop, stronger on the left, and inability to stand on either the toes or the heels. The pupils were unequal, the right being larger than the left; both responded sluggishly to light and in accommodation. The other cranial nerves were intact. All the deep reflexes were diminished; superficial reflexes were present and equal on the two sides; no pathologic reflexes were elicited. Sensation was normal.

There were pronounced weakness in plantar flexion of the foot and toes, especially on the left, weakness of the shoulder girdle bilaterally, weakness of the hand grips and in pronation and supination of the forearms and muscular atrophy. The anteflexors of the head were weak. The sternocleidomastoid muscles were atrophied and were not seen to contract. The orbicularis oculi muscle was weak. The face was smooth, with little wrinkling. Both the masseter and the temporal muscles seemed to be slightly atrophied. A myotonic reaction was noted after squeezing of the hands. No fasciculation was noted.

There was loss of hair over the trunk, extremities and axillas. Distribution of hair over the pubis was of feminine type. The testes were atrophied bilaterally. The fingers were tapering, and the skin was glossy. Both eyes showed cataracts. Biopsy of muscle revealed changes indicative of muscular dystrophy.

Crossed Cerebral Lesions: Left Hemiparesis and Right Honomymous Hemianopsia. Dr. Samuel A. Victor.

A white man aged 47, a bartender, complained of having "bumped into" objects to the right since June 1946, inability to use the left upper extremity since March 4, 1947 and weakness of the left lower extremity since March 7, 1947. The patient stated that in May 1946 he became confused on orders for drinks and forgot people's names. He had episodes of blurring vision for fifteen to twenty minutes. A ventriculogram made in June 1946 failed to reveal any change. The weakness in the left upper extremity and the left side of the face progressed to complete loss of power, followed by weakness in the left lower extremity.

On physical examination the patient was cooperative and easily accessible. The liver was palpable 1 inch (2.5 cm.) below the right costal border.

He was right handed. Examination of the eyes revealed right homonymous hemianopsia, normal fundi and horizontal nystagmus on right lateral gaze. The pharyngeal reflex was absent. There was left hemiparesis (flaccid type) with paralysis of the left side of the face, of central origin.

Laboratory Examination.—The red blood cell count was 5,080,000 and the white cell conut, 11,400; serologic reactions of the blood and spinal fluid was negative. The spinal fluid was under an initial pressure of 220 mm. of water, with a cell count of 4 per cubic millimeter and a negative Pandy reaction. A roentgenogram of the chest was normal. The electroencephalogram showed a focus of slow waves in the right frontotemporal area. A ventriculogram revealed an area of irregular density in the region of the third ventricle and depression and deformity of the anterior and temporal horns on the right side, with suggested midline density and corroborative evidence of spreading pressure in the left lateral ventricle. The findings were compatible with the diagnosis of a mass in the region of the third ventricle.

The impression here is of involvement of both cerebral hemispheres by a primary space-occupying lesion of the frontotemporal area on the right, with extension to the left side by continuity or pressure. Mutiple vascular occlusions (thromboses) should also be considered.

Thrombosis of the Anterior Spinal Artery. Dr. Irving C. Sherman.

A white man aged 64 was in good health until Jan. 3, 1947, when he noted pain in his back and aching in his legs. The following morning his legs were too weak to support him. Within a few hours the righ lower extremity became completely paralyzed, and the left lower extremity was feeble. Subsequently, he was unable to control the bowel and bladder for a few days. He was hospitalized elsewhere from January 7 until March 28, when he was admitted to Cook County Hospital. The past and family histories were noncontributory.

On admission, he displayed spastic paraparesis, involving the right side more than the left. Tendon reflexes were brisk in both lower extremities, being more hyperactive on the right, with inexhaustible patellar and ankle clonuses on that side. The Babinski sign was elicited bilaterally, with Gordon and Chaddock reflexes on the right. Sensation was preserved for cotton, position and vibration. Analgesia existed up to about the eight thoracic dermatome on the right and up to the tenth thoracic dermatome on the left. Perception of cold was lost on the right side up to the twelfth dematome and on the left side to the ninth, with some preservation in the sacral and lower lumbar segments on the right. Perception of warmth was present, but was a little less acute over the legs than over the chest.

The results of laboratory investigations were all within normal limits. The diagnosis was thrombosis of the anterior spinal artery in the lower thoracic area of the spinal cord.

The patient has regained considerable power in the left leg and some in the right. He still has frequent spasms in the right leg. He has regained control of his bowel and bladder.

Subdural Hygroma. Dr. Ben Lichtenstein.

A Lesion of the Brain Stem. Dr. Victor Gonda.

Alcoholic Cerebellar Ataxia. Dr. Leo Kaplan.

INDEX TO VOLUME 59

The asterisk (*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles. and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

THE ARCHIVES OF NEUROLOGY AND PSYCHIATRY is published by the American Medical Association to stimulate research in the field of diseases and disorders of the nervous system and to disseminate knowledge in this department of medicine.

Manuscripts for publication should be sent to Dr. Tracy J. Putnam, Chief Editor, 416 North Bedford Drive, Beverly Hills, Calif., or to any other member of the Editorial Board. Books for review and correspondence relating to the editorial management also should be sent to Dr. Putnam. Communications regarding subscriptions, reprints and other matters should be addressed, ARCHIVES OF NEUROLOGY AND PSYCHIATRY, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones will be supplied by the Association when the original illustrations warrant reproduction and when their number is not considered excessive.

Footnotes and bibliographies (the latter are used only in exhaustive reviews of the literature) should conform to the style of the *Quarterly Cumulative Index Medicus*. This requires, in the order given: name of author, title of article and name of periodical, with volume, page, month—day of month if the journal appears weekly—and year.

The ARCHIVES OF NEUROLOGY AND PSYCHIATRY is published monthly. The annual subscription price (for two volumes) is as follows: domestic, $10.00; Canadian, $10.40; foreign, $11.50, including postage. Single copies are $1.00, postpaid.

Checks, money orders and drafts should be made payable to the American Medical Association.

CONTENTS